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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



JANUARY, 1943

THE PRINCIPLES OF TREATMENT OF CLOSED HEAD INJURY*

D. DENNY-BROWN

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province of surgery, indeed any case may require skilled operative intervention. It may therefore seem odd that a neurophysician like myself should present views on this subject. In defense however I would invoke the authority of no less than Richard Bright, he that first described chronic nephritis, who says "Yet I think it right not entirely to pass over these accidents because they frequently lay the foundation for disease which the physician is called on to alleviate." In that same volume in 1831, Bright¹ proceeds to give the first description of traumatic petechial haemorrhages. The neurologist who has habitually assisted in the problems of severe head injuries may also be expected to have his own views on their treatment.

Closed head injury, for the purpose of this discussion is taken to mean a head injury brought about without break in the scalp. The importance of making this distinction is to exclude the question of treatment of scalp wounds, and penetrating wounds of the skull, which

^{*} Read October 12, 1942 at the fifteenth Graduate Fortnight of The New York Academy of Medicine.

raise an independent series of surgical problems. Since scalp wounds are usually caused by the impact of some sharp edged object, closed head injuries are sometimes spoken of as "blunt head injuries," which we shall assume are the same thing.

At the beginning I would make it clear that head injury, even the subdivision closed head injury, is not a single pathological or clinical entity. Dr. Leary, in his masterly Ludwig Kast Lecture has shown us the variety of traumatic pathological conditions which may reside within the intact skull. It is clear for instance that cerebral contusion, subdural haemorrhage, and extradural haemorrhage can either singly or in various combinations arise without that immediate loss of consciousness which we call concussion. There is good reason to know that alternatively concussion can arise without any haemorrhagic lesion, as was maintained long since by Jonathan Hutchinson² and von Bergmann,³ and demonstrated on an experimental basis by Polis,4 Miller,5 and ourselves.6 Symonds⁷ and Denny-Brown⁸ have also reported instances of medullary lesions without other complications, and Denny-Brown and Russell⁶ have reported instances of skull fracture and cranial nerve lesions from crushing injury without other complication, even concussion. We are not certain of the end point of what we term concussion, of which the clinical signs are largely negative-loss of consciousness and loss of reflexes. As John Hunter9 has said "when there is depression of bone or extravasation the symptoms of concussion are lost, though it may be at bottom of all." I quote this opinion of over a century ago to show that what we consider is no new problem, that it can be as tough now as it was then.

It is not the place here to consider the various clinical states which may be associated with each of these various complications of head injury. Nor do I think it worth while to list each complication of head injury and its appropriate treatment, for the treatment of each singly is well founded and straight-forward. The difficulties encountered in practice are mainly traceable to the admixture of one entity with another, the confusion of signs and symptoms which betokens the mixture in pathology in all severe head injury. Allow me then to consider these mixed clinical states and discuss their treatment in relation to possible pathologies, for this is the way we meet the problem at the bedside.

The most obvious phenomenon in most head injury is unconsciousness. It is a condition which is defined in negatives, the absence of con-

sciousness, the absence of reaction, the absence of memory. In order to make myself clear I shall adopt the classification recommended by the British Committee on Brain Injury¹⁰ and speak of *coma*, as a condition of lack of all reactions except the elementary corneal, tendon and flexion reflexes, of *semicoma*, as being coma with the addition of ability to make simple reply to painful or forceful stimulus, and of *confusion* to cover the lighter degrees of loss of awareness up to and including states where the only defect is one of loss of judgment or lack of appropriate behavior.

The treatment of *coma* begins immediately following head injury. It is associated with loss of all reflexes for an interval, and importantly for first-aiders, with loss of swallowing, so that the first attempts to administer fluid by mouth should be with the head turned on one side so that fluid may run out of the mouth if deglutition does not occur.

In immediate traumatic coma, or concussion of severe degree there is a great fall of blood pressure, with peripheral constriction of vessels, lasting some 10 to 30 minutes. This preliminary shock then passes off rapidly and considerable peripheral congestion with rapid pulse and rapid shallow respirations supervenes. This state need give rise to no alarm, and in simple concussion is the prelude to restlessness and semicoma, finally confusion, leading to recovery. There is little time for haemoconcentration to occur so that in the absence of wounds transfusion is not usually necessary, though moderate warmth and flat posture should be maintained.

In all very severe injuries stertorous and slow respiration, spontancous deviations of the eyes, sometimes twitching of the limbs or face soon occur as the primary shock passes off and indicate that some immediate and grave contusion of the base of the brain or brain stem, usually with massive haemorrhage at the base is occurring. Coma is profound from the beginning and the pulse remains feeble. Such cases seldom survive more than a few hours, and no treatment is of any avail. The temperature may show a precipitate final rise. Lumbar puncture will withdraw darkly blood-stained fluid without relief of symptoms, dehydration makes no difference, nor are the contused vital centres amenable to direct surgical attack. If a head injury is severe enough it will kill, in spite of medical heroics. Such cases account for the high incidence of death in the first two days, as indicated by Jefferson.¹¹

Short of such calamity the profound coma of concussion progress-

ively lightens. The corneal reflexes become more brisk, within two or three hours some reaction to a painful stimulus will occur, and a steady regular respiration is interrupted by such a stimulus. The limbs begin to show postures and occasional movements, the face to wince, and for the first time hemiplegia if present can be observed by the lack of this posture or movement on one side, and the appearance of appropriate plantar response. From this time, which may be from one-half to six hours after injury, the study of these signs will give valuable leads to pathology and then to treatment. In addition we may investigate the spinal fluid. It is likely to be blood-tinged in nearly all injuries with coma lasting more than one hour. The pressure ranges between 200 and 300 mm. in most of such cases. Let us consider three main possibilities:

- 1. Increase in comas, or in signs.
- 2. Increase in lumbar puncture pressure.
- 3. Progressive lessening of all signs and symptoms.

1. Increase in Comas, or in Signs

The classical description of the clinical condition of epidural, or extradural, haematoma includes what is called the "latent interval," a space of mental clarity following head injury, followed by the appearance, or renewal, of stupor. The duration of this latent interval obviously depends on the time taken by the haematoma to raise intracranial pressure to a critical value. If severe concussion has occurred the coma of concussion may last over and merge with the coma of cerebral compression. This however is unusual, for extradural haematoma is caused by localized injury and such severe concussion by generalized injury. In any case the reversal of improvement should be apparent if close watch is kept on physical signs. A dilation of the ipsilateral pupil, a slowing of pulse rate or a rise in blood pressure may be late events, but for that very reason are not so reliable. The change in lumbar puncture pressure occurs in too brief an interval to be of value as a diagnostic. A transverse fracture of the temporal squama may serve to make the wary keep a closer watch on the nervous physical signs. The treatment is purely operative.

More difficult to assess is the more gradual failure in improvement in coma, or gradual late deepening in 24 to 48 hours or even longer, which betokens the formation of an early subdural clot, or a collection of watery fluid ("hydroma" of Naffziger.¹²) The presence of this condition

does not always give rise to increasing hemiplegia or delayed appearance of a dilated pupil, both of which indicate necessity for intervention. More commonly it is associated with the occurrence of a steadily maintained state of semicoma persisting over 24 to 48 hours or even several days. In other circumstances this period is associated with great restlessness, and the stillness and apathy of these patients is a striking feature. There has usually been facial or limb weakness on one side since the time the first movement has been observed. This is not due so much to the haematoma or hydroma as to the contusion and laceration of meninges which gave rise to it. The problem now becomes which is the cause of the lack of recovery, the contusion or the fluid collection? I am sure, both from having been brought up in close association with a conservative surgical school, and from having observed old dural stains and membranes in the autopsy room in patients no longer having any complaint referable to their old head injury, that these acute subdural haematomas and hydromas are by no means necessarily progressive and dangerous as are chronic subdural haematomas. They are seldom seen in autopsy of acute injuries, nor is the severe compression of the brain they might be supposed to cause if they are the cause of death.

Surgical opinion on the subject differs greatly since the classical monograph of Brion¹³ in 1896. Munro¹⁴ is a staunch advocate of early operative exploration in any prolonged unconsciousness. Browder and his associates¹⁵ take essentially the same view, but use ventriculography in doubtful cases. Published figures show a high mortality after such operative relief in the first 24 hours (83 per cent, Laudig, Browder et al¹⁶) or even the first three days (e.g. 9 out of 10, Voris¹⁷). It seems doubtful therefore if the surgical relief of this condition had any effect on the natural course of the severe head injury in this early period. Voris¹⁷ (1941) speaks even of filling the cavity previously occupied by the haematoma with water to induce swelling of the brain!

In relation to a failure of progressive recovery from coma therefore my attitude is conservative, and I would maintain nourishment while watching for change. Should signs of hemiplegia become more marked, or simple coma be steadily deepening, I should recommend exploration. But seldom have I seen dramatic recovery from steadily maintained coma by relief of an early subdural collection of fluid, and suspect an underlying contusion or lacerations to cause persisting symptoms. It is difficult to be convinced that operative relief of an acute subdural lesion

was necessary to save life, and then only when there was rapidly progressive late hemiplegia with very rapid postoperative improvement. It is of interest to find that this view was held by Bergmann and Wiesmann¹⁸ in 1904 and earlier. These authors also note the tendency of these acute lesions to disappear and leave only a dural stain.

I am not convinced that dehydration affects such acute fluid collections though that is a possible rationale which may be advanced for dehydration. Little is understood of the absorption of fluid from the subdural space, but it may be pointed out that these acute subdural collections have little relation to any vascular bed and usually spring from some small tear in the arachnoid.

Also coming into the group of cases under discussion is a type in which some focal signs (usually facial weakness with or without dysphasia) are present immediately following the injury, may progress for an hour or two then remain constant for several days, with slight additional increase between the 5th and 10th days, without further impairment of consciousness. This late increase in signs may be of the order of transition from a slight dysphasia to a complete aphasia. There is usually an increase in blood in the spinal fluid after the first day, but no severe subarachnoid haemorrhage at any time. The inability to exclude the possibility of subdural haematoma usually results in exploration. The surgeon finds no haematoma, but instead a purplish discolored brain in the region of the Sylvian fissure. If the pia-arachnoid is sectioned clots will extrude, and the sucker will leave a great cavity far undercutting portions of frontal, parietal and temporal lobes. The haemorrhage in such cases I have seen explored has always appeared to me to be in the Sylvian fissure, from an oozing subpial and subarachnoid contusion in the region of the middle cerebral vessels. The natural resolution of such a condition appears often to result in better salvage of the neighboring tissue than does operation, and we have not been impressed by the immediate effects of operation.

An important cause of late increase in, or appearance of, coma is fat embolism. This complication is apt to occur on the second or later days, and in relation to pulmonary signs, swinging fever, cutaneous petechiae and fat in the urine. There may or may not appear fresh neurological signs, increase in CSF pressure, convulsions. A stormy and usually fatal illness results, but recovery with or without cerebral residua can undoubtedly occasionally occur. Hunt¹⁹ reports such a case

without residua. Exploration reveals only increased subarachnoid fluid. No treatment affects the course of the illness. Various emulsants have been tried, some resulting in fresh symptoms as if more fat had been released into the circulation.

A possible but rare cause of persistent stupor or confusion is pneumocele, arising from suction of air through a fissure into the frontal sinus in a restless patient. This draws attention to the need for surgical repair of comminuted fracture of the posterior wall of the sinus. Rhinorrhoea from the same cause is a most significant symptom. If it occurs but once in the early stage, and there is but a simple fissure in the bone, I am not convinced that surgical repair is better than the normal dural healing process. But if rhinorrhoea or pneumocele occurs after the first week or if there is likelihood of prolapse of brain into the frontal sinus, surgical repair of the dural opening becomes an urgent necessity in order to prevent subsequent meningitis. It is most important to realize that this can occur in so-called closed head injury.

Last in this group I would mention a most disturbing but fortunately rare event-the occurrence of a delayed traumatic hemiplegia. I have seen two such cases in young men in each of which an original injury to the neck had been overlooked. In one of these a subsequent arteriogram by Cairns showed an occlusion of the internal carotid artery on the side of the lesion. It is obvious that the sequence of events was here damage to the intima of the carotid resulting in progressive clotting and eventual occlusion of the middle cerebral. This explanation could equally well apply to the other case, but with embolic hemiplegia, for the internal carotid was found to be patent, but distorted. In both cases such explanation is preferable to any supposed delayed direct damage to cerebral vessels, but in neither case can effective treatment be suggested. It might be noted in passing that a recent case of delayed hemi-plegia reported by de Veer and Browder²⁰ also suffered an injury to the neck, though the event was attributed to middle cerebral thrombosis. Such delayed hemiplegia should not be confused with the very common delayed facial paralysis of peripheral type which is related to the liquifaction of clot in the middle ear and has an altogether benign course.

2. Increase in Lumbar Puncture of Intracranial Pressure

The lumbar puncture pressure is raised in many cases of severe head injury. The degree of rise is moderate, reaching less than 350 mm. in

almost all. A rising lumbar puncture pressure, plus an increased depth of coma is a combination that cannot be ignored, and requires surgical exploration. On the other hand a moderate increase of CSF pressure with lightening or even stationary coma is of benign significance. The cause of raised CSF pressure is then contusion. Experimentally the course of events in the development of contusion is slow. In animal experiment the disturbance we call concussion may be over by the time the contusion has appeared (Denny-Brown and Russell,6 1941). The immediate increase in pressure is small unless the basilar portions of a hemisphere are injured. Death rarely occurs from simple hemisphere contusion. Oedema surrounds the contused area. This takes several hours to develop, and its development in relation to medullary contusion is the presumed cause of death in the first 24 hours in severe cases without progressive haemorrhage. This reasoning has led to the employment of extensive dehydration by Fay and others. Unfortunately the results are exceedingly difficult to assess.

If we enquire into the reason for this difficulty we find immediately that there are several causes for confusion, and they are chiefly concerned with the definition of oedema, and what we might expect dehydration to accomplish. Thus

a. Oedema is not to be measured simply by increase in intracranial pressure. Thus for instance, the highest and most persistent increases in intracranial pressure are found in cases of occipito-parietal fracture with tearing, and later thrombotic obstruction of the sagittal sinus. I have seen such a case with papilloedema and a very high C.S.F. pressure lasting to the fourth week. There were no other signs and the patient sat cheerfully in bed, complaining only of not being allowed to walk around the ward. The degree of papilloedema was controlled by lumbar puncture until the hydrocephalus subsided naturally in the fifth week, probably from recanalization of the sagittal sinus. It was manifest that dehydration was unnecessary in such a case, that the brain was compressed by external hydrocephalus.

As Browder and Meyers¹⁵ have indicated the rise of spinal fluid pressure in severe head injury seldom approaches the limits of diastolic blood pressure, at which it would begin to constitute a danger. The careful studies of Browder and Meyers have documented clearly what is evident to the careful clinical observer, that the classical signs of dangerous intracranial pressure, slowed pulse and respiration, rising systolic

pressure, are extremely rare, and do not usually herald the approaching end.

It has been shown elsewhere (Denny-Brown⁸) that the most remarkable slowing of the pulse in cases of head injury can occur when there is no question of critical intracranial pressure, and is related to medullary contusion.

- b. It has already been mentioned that a contusion itself by reason of its contained extravasation of blood, increases pressure in moderate degree. This blood extravasation is not affected by dehydration, nor is the loss of nervous function in the area thereby recovered. The initial direct contusion symptoms are therefore not affected by dehydration, and take some 3 to 6 weeks to subside. We cannot expect to heal a bruise by dehydration. Yet it seems that immediate betterment or complete relief of symptoms is expected, or even reported, following dehydration. That can only occur through misconception of pathology.
- c. If dehydration is to have obvious effect its logical place is in combating the progress from deep stupor to deep coma that occurs between the 6th and 48th hour after very severe head injury, and which all are agreed to call "medullary oedema." Occasionally it is a ventricular haemorrhage in disguise. But dehydration, if it has effect, will only restore the stage of deep stupor, or prevent the dangerous worsening.
- d. Dehydration of degree sufficient to be worth while in this connection is not itself without dangers. In all severe head injury there is a period of immediate and profound fall in blood pressure lasting several hours. This appears to be a variety of "primary surgical shock." When there has been exposure to cold a period of secondary surgical shock occurs, as with other wounds, with corresponding haemoconcentration. This condition is in no way benefited by dehydration. There is no information as to the relative interaction of these two in head injury and further studies are badly needed. I can report however that in severe head injury with traumatic delirium I have seen manifest immediate general improvement and subsidence of restlessness, without change in physical signs, with cessation of dehydration.
- e. It is necessary to emphasize that dehydration has no effect whatever on the steadily improving course of mild head injury—except to worry the patient and increase restlessness. Headache of post-lumbar puncture type, hypotonic postural headache, is often a troublesome sequel to unnecessary dehydration.

The place of dehydration therefore is the possible prevention of "acute medullary oedema" and in this it appears remarkably inefficient. In other types of cases there is no clear conception of what dehydration accomplishes. All statistics in this connection are confused by the inclusion of cases of less severity, which in any case run a milder course. Further accurate studies on shock are desirable.

This section of my discussion was concerned with increased intracranial pressure. To identify such increase with a hypothetical "oedema" only blinds us to its varied causes. There is no well founded state of traumatic oedema apart from that accompanying contusion. Let us rather persist in seeking features which will indicate the true pathology which I am sure differs from case to case, but of which the most significant ingredients are contusion, or damage to venous drainage.

3. Progressive Lessening of All Signs and Symptoms

It has been clear since the first writings about head injury by Paré²¹ and others that certain milder kinds of head injury, even with loss of consciousness, undergo a steadily progressive improvement and eventual recovery, without evidence of any persistent damage. To such cases, without other clearer definition the term concussion, or commotion, of the brain was applied. Many have doubted the existence of such an entity, saying where is its pathology, how can such a profound disorder have no pathology. A disorder without histological basis is certainly a challenge, but it must not be forgotten that such well recognized conditions as tetanus, or epilepsy, also lack a histological basis in morbid anatomy. That is not to say that they do not exist. Recently I have attempted to give the condition concussion more concrete definition in terms of nervous function by experimental means (Denny-Brown and Russell,6 Williams and Denny-Brown.22) It is maintained that it is a type of traumatic paralysis which undergoes spontaneous resolution, with perfectly clearly definable sequence of events in terms of the E.E.G. and of reflex function.

The question that has exercised all minds dealing with this problem is "How long can concussion last and still not be complicated by other more serious haemorrhagic lesion?" I would answer, first that concussion is one of a series of components of head injury, and may coexist with any of the others, some of which also cause unconsciousness, so that to my mind the question should be "How are we to know when concus-

sion overlaps with other complications, and for how long can concussion account for unconsciousness?" I put the question in this way because that is how it affects our management of head injury, and because until recently loss of consciousness was the only criterion of concussion.

With the development of electroencephalography and air encephalography it has become realized that there occur a group of cases of prolonged coma followed by delirium and confusion, the whole disorder gradually subsiding in days or weeks, without evidence of focal lesion at any time. Furthermore the generalization of very slow waves in both hemispheres in the E.E.G. in these patients, throughout the amnesic period provides positive evidence of a general pathology. A laceration of the brain shows a local disturbance. Thus there is fairly good evidence that such a condition of traumatic coma and confusion can be due to some generalized physical disorder of the cerebrum rather than to any haemorrhagic lesion. In the absence of increased intracranial pressure, or localizing signs, and in the presence of a generalized slow wave E.E.G. disturbance, coma can therefore be expected to make a slow resolution without operative interference. Dehydration is without effect in these cases. They are primarily a nursing problem, though the restlessness and delirium, particularly at night, requires sedation and the intelligent use of fluids and nourishment. Restraint is preferable to a very heavy sedation over a long period. It is important to exclude distension of the bladder as a cause of restlessness.

In all cases where there is embarrassment of respiration morphine is contraindicated, and chloral-bromide or paraldehyde used. When scalp wounds have occurred and loss of consciousness is no deeper than stupor, British surgeons commonly use small to moderate dosage of morphia to control restlessness. I have never seen disadvantage from such use of morphia, though I am aware of resistance to such use in this country. The effect of any sedation in making changes in the degree of coma must be allowed for.

In such cases, the possibility of subdural haematoma is one that continually exercises the doubts of the attending physician. One useful point is that restlessness and delirium are extremely uncommon in the presence of a dangerous haematoma.

It is of course possible for such a maintained concussive state to coexist with other complications such as haematoma, contusion or laceration of the brain. That these are not more commonly mixed is I think

due to the fact that such lesions as contusion laceration and extradural haematoma result usually from very localized violence, whereas concussion is due to the general shaking of the brain. Few injuries provide both factors in severe degree. But the smaller acute subdural haematoma may complicate concussion. If it does it is seldom of consequence, and no direct lightening of consciousness follows its drainage.

But mixtures of prolonged confused states due to concussion, with the condition called chronic subdural haematoma occur as frequently as with acute subdural collections. In some surgical writings on the subject (Kaump and Love,²³ Holt and Pearson²⁴) it is sometimes assumed that the confused mental state is due to haematoma. In assessing treatment it is important to assess the ingredients of such pathological mixtures separately.

The main principle here is that generalized traumatic coma is a progressively recoverable condition, with slow improvement from day to day. It is useful to have simple means of recording the depth of coma. I would suggest a series of graded tests such as:

- 1. A reaction to a question such as, "What is your name?" spoken in an ordinary tone of voice.
 - 2. An imperative question spoken loudly.
 - 3. The reaction to a painful stimulus.
 - 4. The presence of the corneal reflex.

In this way the change from less to greater reactivity can be more accurately observed.

So slow may the natural improvement be that only by comparing the receptivity and orientation of the patient day by day can the improvement be seen. On the other hand any regression, any loss of ability once regained should lead to suspicion of some progressive haemorrhagic lesion. This is the cardinal principle in treating these cases. Until some means of treatment can be shown to be statistically significant in hastening recovery, or unless there is good reason to suspect a dangerous complication, their treatment becomes that of the management of the comatose or confused patient. A wit has called this "intelligent neglect," but even so I would prefer it to pointless interference.

Apart from the dramatic surgical intervention in the dangerous complications of head injury, the next most important treatment is what might be called "prophylactic psychotherapy." Many forget that head injury is an acute emotional as well as an acute physical crisis. From the moment that the patient becomes conscious, lability of the emotions, lack of confidence and insomnia betray the damage to the psyche. These can and should be met at the time by reassurance and discussion and by rationing of mental effort and excitement. Where post-traumatic amnesia has been prolonged intellectual impairment is to be expected in the convalescent stage and the patient's activities must be graduated within his reduced capacity. With simple psychotherapeutic watchfulness against the patient's secondary anxieties as to his head and his occupation in the early stages much of so-called "post-traumatic neurosis" could be avoided.

Finally, even in quite mild closed head injury, a very labile vaso-motor reaction is extremely common in the first two or three weeks following injury. It is seen chiefly in the form of labile pulse and liability to syncope (Denny-Brown^s) and is due to concussion or contusion of the medulla or upper cervical cord. It is the chief reason for the clinician's empiric insistence on complete rest in bed for this period. Each case must however be judged on its own merits, for head injury is a mixture of so many separate factors, and it is as unwise to keep a very mild case in bed for four weeks, as it is to allow a severe case with prolonged amnesia and confusion up after one week.

Conclusion

It is concluded that the time is ripe for a stocktaking of our present methods of recognition and treatment of the complicated condition we call "head injury." Against some of its chief immediate dangers we have little remedy. The opening days of this century witnessed a famous polemic between von Bergmann³ who maintained that the theory of head injury centered around concussion, and Kocher²⁵ who emphasized increased intracranial pressure. Your own Drs. Browder and Meyers¹⁵ and Munro¹⁴ have assailed Kocher's clinical criteria of compression. I am doubting the vascular factors which were also a vital part of Kocher's theory. In fact I find myself in substantial agreement with most of the views expressed in the last American edition of Bergmann's famous textbook,¹⁵ published in 1904. Let us take this as a challenge and set vigorously to work. It is maintained that a good starting point in clinical practice is more careful gradation and observation of the state we are apt to call "unconsciousness," analysis of which can be a valuable clinical sign.

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THE USE OF VITAMINS IN CLINICAL NEUROLOGY*

The Wesley M. Carpenter Lecture

Neurology, University of Cincinnati College of Medicine

P525252525250 o obtain an equitable understanding of nutritional disease it would seem desirable to have worked in regions when such diseases are endemic. This premiation to be sure, for an incomparison of the sure, for an incomparison of t of any one section of this country, though it is probably not amiss to think that food habits might be. At the least there would appear to be staples of food which are basic in the diet in certain regions of the United States. Examples readily come to mind.

It is within the experience of all of us that allowed choice of food within a certain price range, the dietary does not differ much from day to day. Emotional factors are potent in the choice of food. Astonishing food habits develop of which the habitue is not particularly conscious. To many persons what is eaten is not as important as with whom it is eaten, a point which has more connotations than the obvious one. It is possible that the bonds of habit are as much responsible for the amount of unadulterated nutritional deficiency observed in the southern United States, as is poverty.

Whatever may be thought of this philosophy there will be little argument with the fact that diseases dependent on inadequate ingestion of nutrition are best seen in their elementary form in the southern United States. At the risk of seeming ostentation, it may be observed that one hasn't seen and doesn't understand many of the practical factors of adult human disease incident to malnutrition in this country, until he has served a spell in the South. Certain it is that many of the misunderstandings that surround the subject would be liquidated by such

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experience. One would then be unlikely to include under the heading of human nutritional disorder diseases which are not readily observed in the locales of their greatest incidence.

It has been noted widely that nutritional disease may occur in the face of a normal intake of food. Thus diarrhea, interference with absorption, failure to convert vitamins into absorbable substances, the inhibitory power of infection, congenital requirement for abnormally high intake of certain dietary factors, an increased demand for vitamins to detoxify poisonous compounds, and excessive sweating have been considered capable of producing nutritional deficiency even though the individual is eating normally. Nevertheless the fundamental and best understood nutritional deficiency diseases are those which follow rather directly on the inadequate intake of accessory food factors. Less conjecture surrounds their physiopathology and when neurological disorder develops in their wake, cause and effect appear to be obvious.

If one may dispense with all but a modicum of that emotion which usually wells at the mention of the vitamins, I would like to discuss briefly those clinical neurological states which are benefited by their exhibition. The discussion will be directed chiefly toward therapy. Slight mention will be made of those conditions which are not benefited by vitamins despite reports to the contrary. Finally interesting and provocative investigation on the subject will be touched on. It is obviously not possible to go deeply into any portion of the subject. In the interest of thoroughness the gamut of vitamins will be run, beginning with those of least use in clinical neurology.

Vitamin A

Despite the production of nervous lesions in animals by withholding vitamin A and the hope held forth, particularly in England,¹ that this substance might be of importance in degenerative nervous changes in man nothing has come of it up to now. Wolbach and Bessey² and Mellanby³ demonstrated in young animals deprived of vitamin A that it was the disproportionate growth of the central nervous system in relation to the bone which surrounds it, which caused the nervous lesions.

Since vision is the particular province of the ophthalmologist, a discussion of night blindness and its relationship to deficiency of vitamin A is not in order. It is thought that vitamin A will improve the night blindness of nutritional deficiency.

VITAMIN C AND D

Deficiencies of these substances do not result directly in neurological disorder. The notion that vitamin C deficiency might be concerned in cerebral hemorrhage has not borne fruit.

It has been determined⁴ that vitamin C deficiency is not the cause of hypertrophy of the gums in the dilantin therapy of epilepsy despite the early opinion to the contrary.

VITAMIN E

Clinical work with vitamin E stemmed from the experiments of Einarson and Ringsted⁵ who induced vitamin E deficiency in rats. The deficiency was associated with the development of lesions in the nervous system and muscle.

It is disheartening to have nothing good to say of vitamin E, which has been advocated in the therapy of amyotrophic lateral sclerosis and the muscle dystrophies. Our experience with amyotrophic lateral sclerosis has been just as sad since exhibiting this vitamin as before. Vitamin E has been used in both the natural and synthetic forms, with the disease in its incipiency and also advanced, and in the male and female patient. The gamut of dosage has been run, and it has been administered parenterally and by mouth. Surveying our work with vitamin E, it seems that we have answered every criticism of its adherents, and still found it to be wanting of any beneficial effect in the neurological diseases that beset man. This includes practically all forms of the muscular atrophies and dystrophies.

VITAMIN B COMPLEX

[B₁ (thiamine), riboflavin, niacin (nicotinic acid), B₆ (pyridoxine), paraminobenzoic acid, pantothenic acid, inositol, choline, adenylic acid]

The B complex of vitamins has an established reputation in the treatment of certain neurological disorders. The extent of its efficacy may be explored by systematically considering the neurological diseases of man associated with nutritional deficiency.

It is worth stressing that most, and probably all of the human nutritional deficiency diseases are the result of the deprivation of more than one vitamin. The concept of mixed deficiencies has been repeatedly stressed in the clinical literature by Spies and his co-workers. Wintrobe and his co-workers have put the matter succinctly, "as to clinical observations, the assumption that in beriberi only thiamine deficiency occurs, implies on the part of the victim a knowledge of the distribution of vitamins in foods and an ability to select them which would be exceptional, to say the least."

The most striking response to vitamin B complex occurs in the neuritis of endemic pellagra and in the asthenia, multiple somatic complaints, and acute psychoses which sometimes accompany this mixed deficiency disease.

Neuritis: Neuritis is common in sufferers from pellagra.⁸ It might be advisable to note several characteristics of endemic pellagrous polyneuritis to differentiate it clinically from other forms. The symptoms and signs of pellagrous polyneuritis are of the same kind, though of milder degree than those found in the other varieties. Despite the prolonged deficiency of nutrition which occurs in the great majority of endemic pellagrins, the polyneuritis though longstanding is rarely of great severity. In fact, I have never seen paralyzing polyneuritis in a pellagrin unless he had been ingesting alcohol or had some severe disease of other than nutritional origin.

Pellagrous polyneuritis responds readily to small doses of vitamin B₁ (5 mg. taken orally two or three times a day) if there is normal absorption. There is definite relief; leg pains remit promptly and these patients note strengthening of limbs that had been weak generally. The effect is prompt, usually within days the patient considers cured that part of his complex syndrome. Pellagrous polyneuritis is probably as close as we usually come to the neuritis of endemic beriberi in this country. It is said that neuritis occurs with some frequency rather early in beriberi, and that this type of neuritis if not too well established responds promptly to vitamin B.

It has been thought that the neuritis associated with prolonged ingestion of alcohol is closely akin to the deficiency neuritides. The clinical evidence for their intimate and complete relationship is not beyond reproach. In the first place, the neuritis associated with alcoholism is almost without exception, considerably more severe than the neuritis of endemic, non-alcoholic pellagra, if the latter disease may be used as an example of a typical nutritional deficiency. One cannot account for this severity on the basis that the nutritional deficiency, if this be the

etiologic factor, is more prolonged and profound in alcoholism. There is no deficiency of nutrition as prolonged as that seen in endemic pellagrins. Many of these people and their children subsist on grossly inadequate nutrition practically from the day of their birth.⁹

There is some experimental evidence which bears on the question.¹⁰ Speidel11 noted that an environment of dilute alcohol was deleterious to the nerves in the tail of the living tadpole studied by direct observation, despite the apparent well-being of the rest of the organism. More important he described the restoration of these nerves to normal when the tadpole was restored to its usual environment. Lowry, Sebrell, Daft, and Ashburn¹² observed that thiamine deficient rats on water, without exception developed a neurological disorder before paired, thiamine-deficient litter mates on alcohol or whiskey, in other words, alcohol or whiskey appeared to delay the onset of a neurological syndrome in rats. Their work indicates that the ingestion of alcohol in rats does not increase vitamin B1 requirement. Whether or not they are producing neuritis or another complicated neurological disorder is a moot point. Some investigators¹³ with neurological experience are inclined to believe that the disturbance which develops in rats deprived of thiamine is essentially vestibular in locale. Also, it should be mentioned that considerable species difference exists in the experimental production of polyneuritis. No one has yet reported having produced neuritis in man by the feeding of diets low in thiamine, though many have tried. There is considerable rumor afloat that it has been done but the experience has not been documented.

We are a bit afield from therapy, but this discussion leads directly there. Regardless of whether the neuritis associated with alcoholism is or is not a nutritional deficiency neuritis, its response to thiamine, or to mixed vitamins is indeed disappointing. One may relieve the aching, boring, stabbing pain in these severely paralyzed neuritics, but beyond this relief not much need be expected. If alcoholic neuritis is dependent primarily on a deficiency of nutrition and if it isn't usually readily reversible, enquiry should be made into the wherefore of this irreversibility. Alcoholic neuritis cannot be closely compared from a therapeutic standpoint with a type of neuritis that is known to be due to prolonged nutritional deficiency (pellagra). Another profoundly paralytic form of neuritis, namely infectious polyneuritis, which also is not amenable to vitamin therapy, may be reversed rather completely in a few weeks,

even though its development in some cases apparently requires no less time than does the neuritis associated with alcoholism.

These features of neuritis would appear to indicate that another factor in addition to malnutrition is at work in the production of the polyneuritis associated with alcoholism. Nevertheless a nutritious diet should be given to these patients.¹⁵

It is probable that some common disorder of metabolism underlies all of polyneuritis¹⁶ despite the apparent variance of precipitating agents, although the various clinical types respond differently to the exhibition of vitamin therapy.

Subacute Combined Degeneration of the Spinal Cord: The neuritis which accompanies subacute degeneration of the spinal cord which may or may not be associated with anemia, appears to respond to nothing besides liver extract administered parenterally.

We have had occasion to give brewer's yeast plus large intravenous doses of thiamine (50 mg. twice daily) to patients with posterior lateral sclerosis of the spinal cord associated with pernicious anemia. During the period occupied by this therapy the neurological signs progressed in severity, despite a reticulocyte response and an increase in the number of red blood cells.

Mental Symptoms of Pellagra:¹⁷ In persons suffering from nutritional deficiency there may be a breakdown of the integrating forces of the personality with resultant mental symptoms. Their nature and severity depend on the structure of the personality previous to the disease as well as the intensity, duration, and abruptness of the deprivation of nutriments.

Mild Mental Symptoms: Among the comparatively milder nervous symptoms which may occur early in the course of pellagra, anxiety is an outstanding feature. Anxiety may range from apprehension and restlessness to anxiety attacks with severe respiratory symptoms and fear of impending death. The commonest complaint is nervousness; these patients are easily startled, excited, or irritated. They are sensitive to sounds which normal persons do not find particularly disturbing. They are easily frightened, and they avoid crowds. They feel sad; crying spells are a frequent manifestation. They have difficulty in maintaining attention and in concentrating. Dizziness and headache are common.

These mild mental symptoms of pellagra which in the past had been termed neurasthenia and considered a prodromal phase of pellagra, re-

spond either to thiamine or nicotinic acid. It must be remembered that pellagra basically is due to a deficiency of several essential substances and its complete relief requires more than a single vitamin. The reason for dual relationship of thiamine and niacin in the relief of the acute mental symptoms of pellagra is not explained on the basis of mixed nutritional deficiency. The reason for the favorable response to both of these substances is not known. The experience with a patient is illustrative of the rapid response obtained in undoubted nutritional deficiency disease.

Case 1. A 17 year old girl entered the Nutrition Clinic complaining of pain in the stomach severe enough to prevent sleep, and painful, cold, numb extremities, and bad nerves. The dorsa of the legs and feet had been red and had peeled several times during the preceding three years. Eight months before entry to the clinic she began to experience pain and nausea after eating. She had been nervous for seven months, frightened by noises and sleepless because of gastric distress and fear. She imagined that she heard bells and voices at night, and she had thought that she could see animals during the day. She had refused to be without a light at night, and she was constantly afraid to be alone. She suffered from palpitation and smothering spells, and feared death during these episodes. She was apprehensive of impending disaster for herself and her relatives. She noted impairment of memory. She could not tolerate noise, sudden noise caused starting. Odors produced nausea, and radio music was usually annoying. She had sensations of crawling and stinging in the skin. She was restless, couldn't stand or sit still, and she complained of fatiguability and weakness. She had dizzy spells. She sometimes staggered and at times felt as though she were walking backward. She suffered from headache. She had not attended school for 3 years because of the illness.

The symptoms were corroborated on physical examination, in addition she had tachycardia and signs of mild peripheral neuritis. She was extremely tense, restless, and apprehensive, and the face was drawn and worried, which made her look old.

One hour after the intravenous injection of 50 mg. of thiamine in 4 cc. of physiological saline solution, she was improved amazingly. She was alert and smiling and felt restored. She lost the apprehension and nervousness, and volunteered that if she could remain that way she would be well. The pulse rate decreased significantly. No more thiamine was administered and the syndrome was allowed to develop again, which it did with the exception of calf tenderness, within thirty-six hours. Four cc. of physiological saline solution administered by vein effected no change in her condition. One day later the intravenous injection of 50 mg. of thiamine produced improvement within twenty minutes and virtual "cure" in sixty minutes. She had changed from a state of quiet and morose fearfulness to one of cheerful and playful activity, willing to exchange repartee with the personnel of the clinic. In this instance she was told banteringly that if she did not begin the ingestion of red meats, and other foods rich in the B complex of vitamins, they'd be hauling her away in a box. She replied that she didn't care for that stuff, that "side meat" (pork) and corn pone more nearly suited her tastes. One soon learns the tremendous importance of food habits as well as poverty in the genesis and maintenance of pellagra.

This is the usual course of events in the experimental relief of the milder mental signs of pellagra. The rapidity of the restoration indicates the ready reversibility of the functional disorder underlying the symp-

toms. It is to be noted that neurosis and nutritional deficiency may coexist in the same person. A psychogenic disorder per se would not be expected to be cured by vitamin therapy.

The improvement is of course best maintained on a full, well-balanced diet, in the absence of which it may be fostered by small, oral doses of the vitamin B complex.

Severe Mental Symptoms: Among the most frequent psychotic manifestations of pellagra are confusion, disorientation, impairment of memory, hallucinations, and paranoid trends. The acute psychoses of pellagra usually resemble the conditions sometimes known as toxic psychosis, delirium, or organic reaction psychosis. The relief of the acute psychosis associated with pellagra can be readily accomplished with large doses of nicotinic acid, 100 mg. of nicotinic acid amide hourly during the day, allowing the patient to rest at night. The medication usually has to be given parenterally because of the inability of the patient to coöperate. The attempted therapy of acute and chronic mental symptoms, of other than nutritional origin, with vitamins, has been uniformly disappointing.

The chronic psychoses associated with pellagra are not benefited much by vitamin therapy.¹⁷ The bedridden patient may become more alert and may be got out of bed. The association of pellagra and long-standing psychosis is not common.

Asthenia: In far advanced nutritional disease, particularly in pellagra there occurs sometimes an asthenic condition in which the patient becomes so severely emaciated that one wonders to see him live. These patients complain particularly of weakness, difficulty in walking, irritability, extreme nervousness, insomnia, and abdominal pain, and their gastric condition is such that the stomach no longer tolerates much besides milk. A single intravenous injection of 50 mg. of synthetic vitamin B₆ (pyridoxine) temporarily relieves the weakness and loss of confidence of this peculiar state¹⁸ and may tide the patient over the institution of proper feeding. Possibly the reported efficacy of vitamin B₆ in some cases of Parkinsonism is due to this strengthening effect. A sedative effect has been noted in some persons; sleep being induced with large doses (100 mg.) of vitamin B₆.

Some patients with nutritional deficiency exhibit tremulousness, and slight resistance of the musculature to passive movement. Almost without exception they complain of being weak generally. Should nutri-

tional deficiency be grafted on a case of Parkinson's disease one would not be particularly surprised at temporary improvement with vitamin B_6 . Certainly the two diseases may occur coincidently. However, the usual case of Parkinson's disease is not affected by vitamin therapy.

"Nicotinic Acid Deficiency Encephalopathy": Jolliffe, Bowman, Rosenblum, and Fein¹⁹ have recorded a syndrome characterized by clouding of consciousness, cog-wheel rigidities of the extremities, and uncontrollable sucking and grasping reflexes occurring predominantly in persons chronically addicted to alcohol. Since they instituted treatment with hydration and nicotinic acid they note the reduction of mortality from almost invariable death to 15 per cent in this group.

A comparative clinical picture is not seen in endemic pellagrins. Our experience with patients suffering from "alcoholic encephalopathy" 20,21 indicates that they may improve somewhat with the administration of the vitamin B complex. Usually these persons are so ill that one does not care to risk waiting to see if they would recover spontaneously. All syndromes associated with alcohol addiction tend to improve with the withdrawal of alcohol, and to continue to improve until alcohol again is ingested.

Wernicke Syndrome: The Wernicke syndrome which in most cases is constituted of ophthalmoplegia, polyneuritis, changing levels of consciousness, and mental abnormality, is usually seen in patients addicted to alcohol. It is a non-specific reaction. It has been thought that it may be the result of nutritional deficiency.²² Alexander²³ noted the production of a disease in pigeons by feeding a diet deficient in thiamine, which had as a basis pathologic changes comparable to those observed in persons dying with Wernicke's syndrome. These lesions usually are confined to the periventricular gray matter and are characterized by varicose deformities of the blood vessels and hemorrhage and necrosis in the adjoining parenchyma. Most constantly involved are the paramedian and paraventricular nuclei of the thalamus and hypothalamus, the mammillary bodies, the nuclei of the third, fourth, sixth, and tenth nerves (dorsal nucleus), the nucleus triangularis, and Bechterew's nucleus.

Our experience with the vitamin therapy of the Wernicke syndrome may be illustrated by case reports, which are not selected but represent the most recent cases that have come to our attention. The first patient was closely studied by Doctor John Romano, who has furnished the abstract of her record.

Case 2. A 28 year old woman had been addicted to alcohol for more than five years. Two months before entry to the hospital she developed pain in the calves and burning feet. Three days before entry she became acutely disturbed after a drinking bout. She was tremulous, overactive, disoriented, had sense deceptions, and then fell into stupor. The admission examination revealed stupor from which she could be aroused, mumbling, a poverty of voluntary activity and aimless movements of the extremities when she did arouse, some resistance of the extremities to passive movement, and hyperactive deep reflexes. The eyes could be moved only slightly, and their movements were not coordinated. She developed delirium on the second hospital day, and a Korsakoff psychosis on the third. By the fifth hospital day, the eye movement had improved to such an extent that it was considered to be normal. She had received no nourishment besides parenteral fluid, and parenteral glucose up to that time. She had recovered completely from the psychosis on the sixteenth hospital day, although she had been given no supplemental vitamin products, and had ingested nothing besides the hospital diet. The electroencephalogram which was obtained about every fourth day was grossly abnormal during the early period of her hospital course, improved gradually, and was considered to be normal on the twenty-fifth hospital day. Although she had not received any nutrition besides the hospital diet, she appeared entirely normal and returned to work.

This course of events represents remarkable recovery from the Wernicke syndrome in a young woman chronically addicted to alcohol, the recovery occurring in the face of no therapy other than withdrawal of alcohol, sedation, rest in bed, and the parenteral administration of water and glucose solution. This experience would appear to indicate that the ingestion of alcohol over a long period may be a cause of the Wernicke syndrome.

Case 3. A 32 year old colored female, an alcohol addict of indeterminate standing (many years) was thought to be all right during her rare sober movements, until the morning of admission to the hospital when examination revealed stupor, slurred speech, and disorientation. The eyes could not be elevated or depressed. The left eye could be moved slightly medially and laterally, the right eye deviated slightly downward on lateral rotation which was rather adequate. Medial movement of the right eye was efficient. She could not converge the eyes and there was bilateral ptosis. She had a Korsakoff psychosis and a mild peripheral neuritis. The lateral eye movements improved spontaneously on the fourth hospital day. Thereafter besides the hospital diet, she was given 200 mg. nicotinic acid daily in broken doses, an ounce of brewer's yeast three times a day, and thiamine 50 mg. intravenously for three days followed by 5 mg. three times a day by mouth. This vitamin therapy was continued in the hospital for thirty days without affecting either the remaining signs of the Wernicke syndrome or the psychosis. Three months later while still taking an ounce of brewer's yeast twice a day she remains unable to move the eyes up or down or to converge them; the psychosis is unimproved. She is again drinking heavily.

This experience would appear to indicate that the Wernicke syndrome may not improve over a period of thirty days and longer, with copious administration of certain vitamins of the B complex.

Case 4. A 50 year old white man noticed fatigue and increasing weakness four months before his admission to the Cincinnati General Hospital. He lost his appetite and had several bouts of vomiting. These symptoms had progressed in severity until

four days before hospital entry when he had to take to bed. On the third day he developed diplopia, strabismus, vertigo, unsteadiness, and he himself noted that he couldn't cerebrate normally. The feet and legs developed numbness and tingling, and the tongue was sore at the tip. The patient had had gastric symptoms for longer than 15 years; he had been a heavy imbiber of alcohol up to five or six years ago. His dietary had been restricted for years. The admission examination revealed considerable unsteadiness, the patient would not sit because of it, preferring the recumbent posture. Memory for recent events was poor, he confabulated and expressed a few paranoid ideas. The eyes rested at the inner canthi ("crossed"), and there was gross nystagmus when he attempted to move them. There were signs of mild peripheral neuritis in the lower extremities. All movements of the extremities were unsteady. The tongue was swollen, fiery red, and the papillae smooth. There was no skin eruption.

On the day of admission to the hospital he was given 3 ounces of brewer's yeast and 50 mg. cevitamic acid; and 100 mg. of thiamine parenterally in four doses of 25 mg. each. The strabismus and neuritis remitted promptly, but he developed considerable delirium and then the Korsakoff psychosis. Niacin amide was then administered in 100 mg. doses every hour. The severe psychotic symptoms remitted after he had received 1000 mg. of this substance. He promptly sat up in bed, read the paper, and appeared to be rational. Recent memory defect remained as did the nystagmus.

This experience would appear to indicate that the Wernicke syndrome may result from nutritional deprivation. The psychosis was considered to be an accompaniment of pellagra, which was the diagnosis in this patient, since it responded with such speed to niacin.

Case 5. A 63 year old white woman had had episodes of vomiting monthly for 17 years. They had become more frequent as time passed until they occurred practically after each meal for the week before admission to the hospital. For three months there had been ringing and buzzing in both ears, since then she had gradually lost her hearing until she became completely deaf. She had complained of boring, occipital headache for several months. For one week before admission she had not talked much. Five days before entry she took to her bed. Two days later she became incontinent of urine and feces, and had auditory hallucinations and complete loss of recent memory. Mild psychic signs (confusion, memory loss) had been present for two months. Two days before admission she ceased eating, had jerking movements of the eyes, and was drowsy.

On the admission examination she was somnolent but not stuporous; she waked up readily to coöperate, the tongue was smooth, the heart was enlarged, the blood pressure was 140/90 and there was pitting edema of the lower extremities. The skin of the legs was extremely thick and corrugated and contained patches of discolored scaling (chronic edema). The abnormal neurological findings were an inability to move the eyes upward or downward more than infinitesimally, and convergence of the eyes was impossible. She had difficulty maintaining lateral deviation of the eyes, which was accompanied by coarse nystagmus. Nystagmus was seen with the eyes in a neutral position, at rest. There was moderate bilateral ptosis. There was complete bilateral deafness. She could not bear a tuning fork placed anywhere on the skull. One could obtain coöperation with mimicry; she could not hear shouted requests. She was mildly and generally weak. She did not tolerate applicator stroke in the lower extremities because of the pain it caused. Further sensory tests were not attempted. No tendon reflexes were obtained in the legs and the plantar responses were bilaterally extensor in type. She had sucking and snout reflexes, but a normal jaw jerk, and no Hoffmanns.

Because of the severe involvement of the eye movements (the upward and downward movement of the eyes was reminiscent of limited skew deviation), the bilateral deafness and bilateral pyramidal tract signs, she was considered to have a tumor im-

pinging on the quadrigeminal plate. The similarity of her findings to those of pineal tumor were discussed, and the possibility of the Wernicke syndrome was mentioned.

Because her condition was somewhat urgent she was given 50 mg. of thiamine and 100 mg. of niacin by mouth daily for four days, then 50 mg. of thiamine intravenously twice a day for three days. On the second hospital day, 24 hours after vitamin therapy was begun she was able to move her eyes better in the vertical plane. The eye movements continued to improve until they were of normal excursion on the fourth hospital day. At this time the oral administration of vitamins was supplanted by the intravenous injection of 50 mg. of thiamine twice daily for three days. She was alert within 24 hours after the initiation of parenteral therapy, but it was now not difficult to elicit the signs of a Korsakoff psychosis and moderately severe peripheral neuritis. The day after the intravenous therapy was begun, she could hear the slightly raised voice. An audiogram done on the seventh hospital day revealed a 55 per cent loss of hearing in either ear. She has continued to have the signs of severe mental deterioration which were immediately demonstrable on her spontaneous arousing from stupor on the fifth hospital day. Her hearing had continued to improve slightly. We are at present supplementing the hospital diet with 5 mg. of thiamine three times daily, and 100 mg. niacin amide six times daily.

A thorough history in this case was available from the daughter, who lived with the patient. She had drunk two to three quarts of beer daily for about thirty years, using it in place of water. She took no strong alcoholic beverages. The patient was something of a food faddist. She ate practically no meat, eggs, cheese, or butter. She ate sparingly of bread. She drank considerable sweet milk, chocolate milk, and buttermilk. She had gradually reduced her food intake over the past year and for about nine months had eaten little, subsisting chiefly on liquids.

The dramatic improvement in hearing from total deafness is noteworthy particularly in light of Selfridge's²⁴ report of quantitative improvement in hearing with niacin administration. We had noticed some slight improvement in the hearing of some pellagrins receiving vitamin B complex but had thought that it was due to increased alertness.

It is possible that this patient's improvement would have occurred spontaneously, and the same may be said of Case 4.

It is apparent that in man at least, the Wernicke syndrome may be associated with prolonged alcoholism or with undoubted nutritional deficiency. In our experience the former is the more frequent. The Wernicke syndrome is not a frequent occurrence in any case; in the Nutrition Clinic at Birmingham its occurrence has been observed possibly twice in over 2,000 cases of nutritional deficiency. The term possibly is used since the diagnosis was uncertain in one case (Aring et al, ¹⁰ Case 3). The patient was a 45 year old woman who had had the first attack of pellagra in 1925. She drank no alcohol. She had suffered an old injury to the right eye at the age of 10 which had resulted in blindness, and abnormal pupillary reaction in this eye as well as external strabismus. No lens was present in this eye and there was a membranous secondary cataract, hippus, and posterior synechiae. The signs which might

have been considered as part of the Wernicke syndrome were partial bilateral ptosis, and considerable limitation of upward gaze. Neither of these signs improved after the use of much Vitamin B₁ administered parenterally and orally.

It may be surmised from these case reports that a patient may make a spectacular recovery from the eye signs of the Wernicke syndrome with vitamin therapy, that he may recover apparently spontaneously, or that he may make no improvement despite vitamin therapy. The latter experience has not been uncommon at the Cincinnati General Hospital. We may predicate reversibility and irreversibility without saying anything.

The alert physician who sees this syndrome will try vitamin therapy parenterally at first, but he will not promise too much and thence will not have to retract, or be forced to see things which do not exist. It is unusual for the evidence of associated mental deterioration to clear with the administration of vitamin B.

Korsakoff Psychosis: This non-specific syndrome is characterized by disorientation, memory defect with difficulty in retention and recall, and confabulation. It may be associated with peripheral neuritis. It usually runs a chronic course with permanent mental changes. The Korsakoff psychosis does not respond to the administration of vitamins.

Delirium Tremens: The course of delirium tremens is not altered by vitamins.²⁵ After reviewing the literature of the late eighteenth and early nineteenth century, Romano²⁶ noted that the prognosis then as now was good in delirium tremens if alcohol was withdrawn and a sedative administered. He concluded that no improvement had been made in the rational treatment of delirium tremens in over a century with the exception of the boon of paraldehyde and a wider awareness of the psychological factors of the disorder.

Migraine: I have had no experience with the use of vitamin B in migraine. It has been noted that good results may be obtained with an average monthly dose of 350 to 450 mg. of thiamine given parenterally, with initial injections of 30 to 90 mg. given daily. The frequency of injection was reduced over a period of about three months. If no favorable result was obtained in four weeks, 15 U.S.P. units of liver extract were administered parenterally once or twice a week. To terminate a migraine attack 60 to 120 mg. of thiamine were given intravenously or intramuscularly.

It is unusual that such prolonged vitamin therapy is necessary in an active disease. Those cases of migraine noted by Palmer²⁷ were of extreme severity as far as pain and frequency of attack were concerned. It has been the experience of those working with vitamins that efficacy is obtained quickly if it is to be had. Another oddity about the migraine patients which Palmer has observed, in addition to those treated with vitamins, is the comparatively low incidence of benefit (58.8 per cent) obtained from the use of ergotamine tartrate.

The Lesser Members of the B Complex from a Neurological Standpoint: Riboflavin deficiency has not been found to produce neurological symptoms, although it may manifest its association by inflammation of the lips, the formation of fissures at the angles of the mouth, glossitis, dermatitis, and vascularizing keratitis.

Paraminobenzoic acid, pantothenic acid, inositol, and choline have been used in neuritis and subacute combined system disease in man usually without effect. Since a lack of pantothenic acid and pyridoxine in the diet of pigs is associated with abnormal gait, degenerative changes in the peripheral nerves, posterior root ganglia and posterior columns of the cord,²⁸ these substances need further evaluation in human deficiency disease.

Adenylic acid is present in high concentration in yeast and crude liver extracts, and like thiamine and niacin, is an organic catalyst essential for cell respiration. Because of the suggested relationship of adenylic acid and vitamins of the B complex, it might be of importance in nutrition. There is some evidence²⁰ that it may be of use in the therapy

of nutritional deficiency neuritis.

Quiescent Brain Lesion Unmasked by Thiamine Deficiency: The work of Odom and McEachern³⁰ appears to be of considerable importance, and it should be repeated promptly in the various species. These investigators placed cats with old surgical brain scars on a thiamine deficient diet. These animals showed no clinical evidence of neurological deficit until it was unmasked by vitamin deficiency. Then signs referable to the portion of the brain damaged made their appearance, and regressed promptly with the parenteral injection of thiamine.

The unmasking of brain deficit is of peculiar importance to neurologists. If one may speculate in another species from these results, they may explain the reported relief of some neurological symptoms in man which are not the direct result of nutritional deficiency. It should

be remembered that there is considerable bilateral representation of function in the hemisphere of the cat. If all tissue is dependent for health on thiamine, presumably a defect in one cerebral hemisphere might manifest itself by the decompensation that is occurring in the opposite healthier hemisphere, which under ordinary circumstances was able to cover the deficit. We know relatively little about the mechanism for compensation in hemiplegic deficit. Presumably in the case of cats, transhemispheral connections are susceptible to thiamine deficiency. One awaits the pathological studies in their cats.

The work of Odom and McEachern supports the concept of irreversibility in nutritional deficiency, since animals whose deficiency was remedied with ease during their first episode of deficiency, were not so readily relieved after a second episode. In cats undergoing thiamine depletion more than a single time, improvement occurred much more slowly and some residual weakness and incoördination remained despite repeated daily injections of thiamine. Repeated thiamine depletion frequently resulted in death.

General Considerations: There are a few simple concepts about the use of the vitamin B complex, the only vitamin which is of much use in neurological disease. Whether the disease is the result of a primary nutritional deficiency, or a neurological disease unmasked by a secondary deficiency, the response to vitamin B complex therapy if it is to occur, occurs promptly (usually one to two days, sometimes three to seven days). These vitamins should be administered in large doses parenterally (thiamine 25 mg. three times a day; nicotinic acid 100 mg. six times a day; nicotinic acid amide, if no vasodilatation is desired, 100 mg. six times a day; vitamin B₆ 50 mg. twice a day) in the early days of the therapy. There is no convincing evidence that one can overdose with these substances, although a financial overdose to the patient should be a consideration. When the desired result is initiated oral therapy may be resorted to, expecting improvement to continue with maintenance dosages if absorption is normal (thiamine 11/2 to 2 mg. daily, nicotinic acid amide 15 to 20 mg. daily, vitamin Be (pyridoxine) dosage unknown). Physicians should familiarize themselves with what is considered to be a generous, well-balanced diet31 for which a few vitamins are not a substitute.

Since the evidence indicates that favorable clinical and experimental response is prompt to vitamin therapy, it follows that advice urging

that patients be saturated with vitamins for months before results can be expected should be examined with considerable criticism. Even if the disease be of the so-called irreversible type, it seems futile to pour the vitamins into the body for a prolonged period, particularly when the patient apparently is ingesting an adequate diet.¹⁴ The therapeutic test should not be withheld, but there appear to be quite definite limits to its significant duration. The nutritious diet should never be lost sight of.

Certain pharmacological properties that might evolve on the use of the vitamins should be considered, since such effects may have nothing to do with nutritional deficiency. Thus niacin is a potent peripheral and cerebral vasodilator^{32,33} and might conceivably be effective wherever vasodilatation is beneficial. The use of niacin in trigeminal neuralgia³⁴ is based on its property of vasodilatation. Niacin amide does not cause vasodilatation.

The factor of deprivation of several nutritional elements should be stressed in neurological disease due to malnutrition. Therefore the administration of a single vitamin in the therapy of these conditions is not a sound procedure. The best method of administering a number of vitamins parenterally is to give liver extract intramuscularly. The maintenance dose of this substance in subacute combined degeneration of the spinal cord under control is 15 U.S.P. units of purified liver every four weeks, which might be used somewhat as a guide in cases of nutritional deficiency. The dose should be graded upward to coincide with the severity and acuteness of the illness. In any case the oral or parenteral use of vitamins is not a happy substitute for the generous, nutritious diet.

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SPEECH DISORDERS AND THEIR TREATMENT*

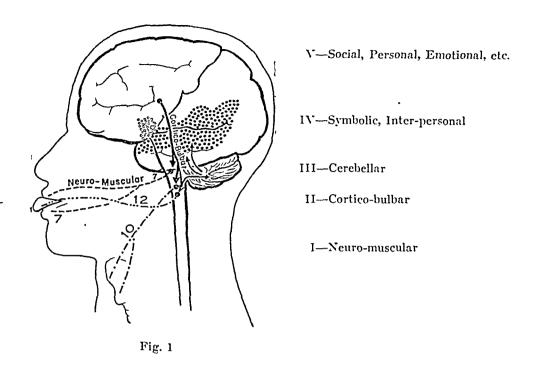
STANLEY COBB

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order to understand speech disorders, one must know something of the development of speech in man and his ancestors. In phylogeny there is evident a close relationship between the development of binocular vision, manual skill, and finally a leading hand and leading cerebral hemisphere. When man's shrew-like ancestors took to trees and left behind them quadrupedal locomotion, their fore-limbs were emancipated to become hands, and the possibility of dexterity developed. Other vertebrates specialize and reach narrow superiority by unique development of one type of sense organ. Man excels because of lack of specialization. His speciality is a leading hemisphere, evenly developed in the reception and elaboration of all types of sensory impression. It is this even development that allows for association between the different sensory receiving stations; and it is the development of the mechanism of association that has made intellectual behavior possible. The dominance of the left hemisphere is marked in right-handed people, who constitute about 75 per cent of the population. The functions are probably not confined to the left hemisphere; the dominance is relative. Recent studies have shown that even speech is subserved in a rudimentary way in the right hemisphere of right-handed persons. With a leading hemisphere in which there is a predominant centering of manual skill (eupraxia), symbolic understanding (eugnosia), and language, there is a great need of many associative tracts. The function of language needs both eupraxia and eugnosia, in fact, each needs the other two for effective behavior. Nevertheless it can be taken as a proposition that language is the most highly integrated of man's functions. 1,2,3

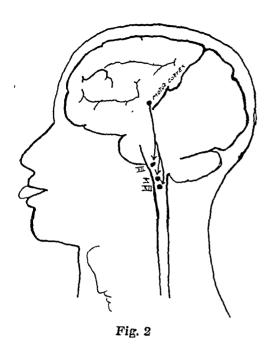
In the central nervous system of man, speech is integrated at five important levels; these are not exact, and to some extent overlap but for purposes of exposition Fig. 1 shows the main centers involved. The

^{*} Given October 20, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.



broken lines show the lowest level, the neuron from a nucleus in the medulla (seventh, tenth or twelfth) to a peripheral organ of speech, lips, tongue or larynx. This is level I, the neuromuscular neurons and the final common paths over which all nerve impulses concerned with speech must pass. Level II is the neuron arising in the motor cortex and ending in the medulla around the bulbar nuclei (seventh, tenth and twelfth), its fibers pass down the corona radiata, through the internal capsule to the peduncles and medulla. This, too, is a common pathway for all the complex speech integrations of the higher levels. It is closely correlated for motor speech production with the cerebellar paths (Level III) which run up from the medulla to the cerebellar cortex, thence to cerebellar efferent nuclei and upward to mid-brain, thalamus and motor cortex. This makes a loop and supplies the mechanism of coördination so greatly needed in the control of speech. These three levels can be considered together as a rather straightforward motor mechanism.

Moving up to Level IV is a big step, for symbolization and meaning come in here. The anatomical localization is cortical with intricate association fibers between the different parts of the speech areas (dotted on cortex of Fig. 1). The circular stippling indicates the motor speech area (Broca), the black stipples show the auditory and visual areas of langu-



LEVEL II-CORTICO-BULBAR

Common Lesions: Syphilis (G.P.I.), Cerebral Arteriosclerosis

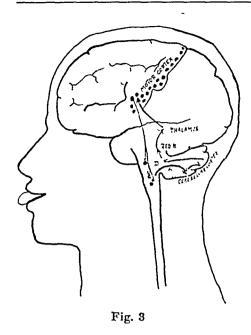
Clinical Results: Dysarthria, Weakness, Paresis or Partial Paralysis

Treatment: Antiluetic or none

age functions and their subsidiaries. These areas are well developed in only one hemisphere, the "leading hemisphere," usually the left. The degree of dominance is important.

Level V is the most highly integrated and least localizable. It is associated with the great association area of the frontal and parietal lobes. It brings in memories, individual life experiences and the impact of one person upon another including the varied and important emotional reactions expressed by glands, smooth muscle and skeletal muscle. The visceral expressions are mediated by the hypothalamus and the autonomic system; the overt behavior responses are expressed largely by skeletal muscles as behavior. Although both may express emotions, they are not the sources of emotion, which must be looked upon as largely cortical, individual and extremely complex.

Taking up each level in turn in regard to (a) common lesions, (b) clinical results of these lesions, and (c) treatment, one finds little of interest in level I. The lesions are usually the obvious developmental defects of the end organs treated by surgery, e.g., hare-lip and cleft palate. Tying down of the tongue by a short frenulum is emphasized by some but is actually a rarity. Trauma and neuritis may paralyze the nerves. Surgical anastomosis may be necessary. Poliomyelitis or more rare degenerative diseases may cause nuclear lesions and, hence, bulbar



LEVEL III-CEREBELLAR

Common Lesions: Multiple Sclerosis, Tumor, Encephalitis

Clinical Results: Incoordinate Speech, Scanning, Monotonous, Flat, Explosive, Staccato, etc.

Treatment: Possible Removal of Tumor; Usually None

palsy. Treatment is unsatisfactory; excessive doses of vitamins may be tried.

At Level II the cortico-bulbar neurons are found to be frequently affected by syphilis, as in dementia paralytica ("G.P.I.") and by cortical softenings from arteriosclerosis. Other pathological processes, such as tumor or encephalitis lethargica, rarely damage these neurons in a selective way. The result of injury to the nerve cells of the motor area which innervate bulbar speech mechanism is weakness, partial paralysis. It is partial because the innervation is bilateral, neurons from one motor area going to the nuclei on both sides of the medulla, although, predominantly to the opposite side. The clinical symptom produced by this weakness is dysarthria or slurred speech. The classical example is the patient with "G.P.I." who cannot enunciate "Methodist episcopal" but says something like "Methyst epistople." The treatment of this sort of bad enunciation is unsatisfactory. Antiluetic treatment sometimes brings back paretics' poor speech. Usually little or nothing can be done. The slovenly speech of uneducated persons must be ruled out by repeated trials of different test phrases and attention to other clinical symptoms.

The third level (III in Fig. 1) is elaborated in Fig. 3 to show more details of the cerebellar coördinating mechanism. Nerve impulses from cells in the medulla enter the cerebellum over afferent tracts (A) bringing in proprioceptive information, data as to what the muscles are doing.

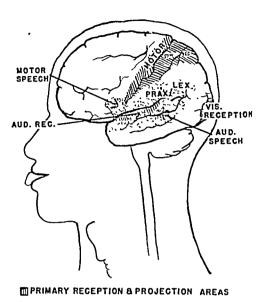
This is spread through the cerebellar cortex by the plentiful association fibers. Impulses then leave the cortex of the cerebellum and go to dentate nucleus (D) whence they are relayed upward through the red nucleus to the thalamus. From here another neuron takes them to the motor cortex of the cerebrum where they have their effect on the motor impulses sent out from headquarters. Impulses from the roof nuclei of the cerebellum and from the red nucleus probably go directly down to brainstem and spinal centers to effect further motor control. Thus a loop or series of loops, is formed for making the delicate motor adjustments of speech all work together. The mechanism is for coördination or synergia.

Lesions anywhere along this pathway will cause trouble. The commonest to disrupt smooth speech are those of multiple sclerosis and epidemic encephalitis; tumors and softenings may also do the same. The clinical results are incoördination (asynergia) of speech, shown in the monotonous speech of Parkinson's disease (where the lesion is probably up near the thalamus), in the scanning speech of multiple sclerosis, and in the various explosive and staccato forms of speech found in encephalitis. Except for the rare removal of tumors, treatment is of no avail.

Level IV is divided in two parts (a) and (b) because (a) takes in the functions of the dominant, leading hemisphere, those functions which are largely absent in the minor hemisphere, while (b) is the relationship between the leading and minor hemispheres. It deals with the degree of dominance of one over the other.

Level IVa (Fig. 4) is concerned with symbolism. Symbols must be sensed, recognized and understood as meaning something. The senses important to language are vision and hearing, each has three levels of integration. Visual reception is localized in the occipital pole and visual recognition in the stippled area just anterior to this. A lesion at the first level causes blindness; at the second, loss of recognition of perceived objects, in other words, visual agnosia. A lesion farther forward, but still behind the angular gyrus (Lex Fig. 4) causes visual disorientation. The patient cannot remember the plan of a house, or he gets lost, although he may recognize the street or house he is seeing at the moment, because he cannot bring back series of pictures.

The auditory sense has three similar levels in the temporal lobe: auditory reception (AUD. REC., Fig. 4), auditory recognition of noises



RECOGNITION, SYMBOLIZATION AND LANGUAGE

Fig. 4

LEVEL IVa-SYMBOLIC

Common Lesions: Arteriosclerotic Softening, Tumor and Trauma

Clinical Results: Deafness and Blindness, Apraxia and Motor Aphasia, Visual and Vis. Verbal Agnosia, Auditory and Aud. Verbal Agnosia, Agraphia, Amusia, Acalculia, etc., Semantic and Amnesic Aphasia

LEVEL IVb-LATERAL DOMINANCE

Common Lesion: Unknown, Inherited

Clinical Result: Slow Reading, Reversals, etc., Stammering, Ambidexterity

Treatment: Retraining by Reading, Speaking, Writing, etc. (Orton)

and auditory recognition of symbols (words). Since the innervation of the temporal lobe is bilateral, a single cerebral lesion does not necessarily cause complete agnosia, and only bilateral lesions can cause deafness. Acoustic agnosia for sounds is not known to occur without some acoustic verbal agnosia, but in many cases of the latter the recognition for sounds is retained. Thus it is obvious that the acoustic mechanism is more variable and less unilaterally dominant than the visual mechanism. Recognition of learned symbols for words seen is in the angular gyrus, (Lex Fig. 4), and a lesion here causes visual verbal agnosia. The patient cannot read, he has "alexia" or "word blindness," as opposed to the "word deafness" resulting from a lesion in the temporal lobe.

Motor dysphasia* is equally complex and depends on an understanding of the fact that no learned motor skill can be practiced without an ideational plan. This is a psychic elaboration necessary as a precursor to the carrying out of any complex motor act. This ideational planning is called eupraxia; the normal person knows how to do a thing quickly and almost automatically when requested. A defect of such performance in response to command is apraxia. It is a symptom of injury to the sensorimotor elaboration areas of the cortex, corresponding to

Dysphasia, meaning disturbed language, is more accurate in most cases than aphasia, which means lack of language

agnosia from a lesion in the more strictly sensory area. In relation to most performances eupraxia is bilateral, the acts of one hand, for example, being planned in the opposite precentral and supramarginal gyri (between PRAX and LEX, Fig. 4). Lesions of these areas or their fiber connections may cause dyspraxia or apraxia.

Apraxia of the organs of speech (tongue, lips, larynx) causes "motor aphasia"; the patient loses the memory of how to make the movements to articulate words; he may know just what he wants to say, but he cannot get the plan of the word into his mind. A lesion of Broca's area (MOTOR SPEECH, Fig. 4) causes this symptom. As a rule only propositional speech is lost when the major motor speech area is injured. This is because the function of language is largely, but not entirely, concentrated in the leading hemisphere; a primitive sort of speech (emotional, expletive, habitual) is subserved in the homologous areas of the minor hemisphere. Individual variation in relation to the degree of handedness is important.

The angular gyrus has the function of symbolic visual recognition, i.e., understanding letters and words by sight. Because words were first learned by hearing, however, this area cannot function if cut off from the temporal lobe. During the process of learning to read, words are sounded out or told to one. Thus the portion of the temporal lobe lying behind "Aud. Speech" (Fig. 4) is of great importance. A lesion here may cause as much loss of reading ability (alexia) as a lesion directly in the angular gyrus. Moreover, because language is learned by associating vision and hearing with objects and symbols, this area is particularly important, Nielsen⁴ calls it "the language formation area." Take, for example, the case of objective nouns, the simplest and commonest words used. They are names, usually of objects seen. So memories must be stored in the posterior temporal lobe correlating both visual and auditory meanings. That this is true is shown by cases of temporal lobectomy in which the language formation area of the leading hemisphere is removed. The result is amnesic aphasia. The patient has lost the storage mechanism for nouns; his "naming center" is gone. When shown a pen, he uses circumlocution and may reply "It's to write with" but cannot say "pen."

If one takes these main symptoms (which are well explained physiologically), agnosia, motor aphasia and amnesic aphasia, and adds the obvious complications, it is seen that many special sorts of aphasia are

possible. But by sticking to the principles laid down, these strange phenomena can largely be explained and localized. For example, one can hear music as well as words; therefore "amusia" is found. One can learn several languages and have marked aphasia in one but little in another. Symbols used for mathematics are different from letters; so one may have agnosia for figures. In fact, loss of the ability to calculate is found after lesions in various areas. Semantic aphasia should be mentioned because it is the commonest of all aphasias and is not localizable. It consists of a quantitative reduction in the capacity for and comprehension of speech. The victim has a little of all language functions left but cannot put sentences together or express any complex idea. This phenomenon is present in persons with diffuse cerebral lesions, commonly senile, in toxic patients and in normal but excessively fatigued persons. In fact, almost all patients with aphasia have an element of the semantic form, and careful examination will usually show some mental loss. Semantic aphasia is a form of dementia.

The lesions causing dysphasia and dyspraxia are varied, the commonest being trauma, tumor and softening. Treatment is often not pushed as much as it ought to be. When the first shock of the lesion or operation is over, and the patient is comfortable, re-education should be started. First comes accurate diagnosis,* because the physician must first find out what parts of the language mechanism remain intact in order that he may work on and through these normal or less injured parts. Of course it is equally important to learn how much language the patient had before his cerebral lesion. Was he a laborer with a vocabulary of only a couple of thousand words in one language? Was he a waiter with glib use of five languages, or perhaps a college professor with many thousands of words in two or three languages? The diagnosis and prognosis differ in each case.

Having discovered what sort of a person one has to deal with and what is left of the cerebral speech mechanism, one can outline treatment. If the aphasia is complete there is little to do but to stimulate the patient to more activity and more contact with environment by moving about and occupational therapy. As speech begins to return a place may be found for the entering wedge of treatment. If the case is one of dysphasia ingenuity must be used to make up exercises which will be understood and will re-educate injured cerebral areas or educate the

^{*} The best short method is that of Cheser, E. C., Bull. Neurol. Inst. New York, 1937, 6:134.

unused area in the minor hemisphere. The evidence is fairly good that the latter is what probably takes place.

For example a patient with visual agnosia cannot recognize objects by sight; he must be shown objects and then be given the cue as to what they are by touch and sound. He looks at the object, feels it and hears the name all at once, and repeatedly. If he has a motor dysphasia with agraphia he is taught to write with his left hand from copy and from dictation. Also he practices speaking words by naming objects while writing the name. The training work is best done by non-medical teachers who have learned the methods in general and who have had from the neurologist special instruction for each case. Goldstein⁵ in his recent book shows how varied are the problems and how ingenious the physician must be in planning the therapeutic attack. It is certain, however, that much can be done, especially in young and middle aged people. The teacher must be patient, go slowly and not work long at any one session. A few minutes often tires the patient.

There will be many cases of dysphasia among the many soldiers with head wounds. The specialists in this line of treatment are few and they should begin now to train assistants and teachers to carry out the re-educational procedures. Moreover, many old people with vascular lesions of the brain would be benefited by these methods of treatment, yet most of them are looked upon as hopeless.

Level IVb is actually the same level of structure and integration as IVa, but it deals not only with the function of the dominant hemisphere, but with the relative dominance of the two. Which is dominant and to what extent? In other words there is no 100 per cent use of one and o of the other; most persons are very largely right- or left-handed, but 10 or 15 per cent of the population are ambidextrous, have no clear dominance and thus have a lack of leadership in the initiation of speech, writing and reading. There is a mixed lead. One result may be hesitant speech and stuttering; another may be reversed symbols and "strephosymbolia" as described by Orton⁶ where letter symbols are confused when similarly formed but differently oriented, as "d" and "b," or words such as "was" and "saw." The left-handed child would like to read from right to left but unfortunately in a right-handed world the books are not printed that way. Uncertainty of dominance is much more common in infants than later in life when habit has settled the question. In other words a tendency to right or left handedness is inherited and is only consolidated by habitual use of one side as a leader. In spite of the fact that handedness is inherited, and therefore dependent upon the structure of the genes, no difference can be seen grossly or microscopically between the right and left hemispheres of the brain.

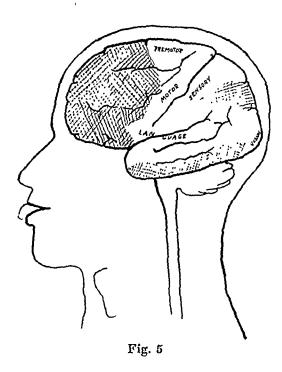
Physiologically it is obvious that one hemisphere leads in normal persons, but lack of clear dominance occurs often. Clinical evidence is impressive that this mechanism of "mixed leads" causes speech and read-

Physiologically it is obvious that one hemisphere leads in normal persons, but lack of clear dominance occurs often. Clinical evidence is impressive that this mechanism of "mixed leads" causes speech and reading defects. Final proof seems to have come from the laboratory, where Lindsley made electroencephalograms of normal people and stammerers during speech. In normals the alpha rhythm of the brain waves was usually synchronous and smooth. In the stammerers the waves in the tracings from the two hemispheres were frequently out of phase and often obliterated, especially when blocking in speech was observed clinically.

Orton's method of training,⁶ aimed at making the patient fix his lead in a chosen hemisphere, is an advance in therapy. One must not, however, think that every ambidextrous child will have difficulty in symbolization; perhaps 10 per cent of the population is somewhat ambidextrous and only about one per cent have difficulty. It is probable that ordinary childhood development takes care of most of the cases; habit and use cure the defect; the child "outgrows" his slight disorder. In the cases where the trouble becomes worse and lasts into adolescence and adult life, to become a real disability, one must look for additional causal factors (see level V).

From the standpoint of treatment, it would seem wise to let a left-handed child work out his own salvation. Do not force him to be right-handed in any way; the world will do that gradually because it is a right-handed world the child is born into. The ambidextrous child needs more care; probably he will choose his lead at an early age and follow it, but if reading or speech difficulty develops, he will need visual, auditory and proprioceptive training along Orton's lines to make one hemisphere (preferably the left) clearly dominant. The great desideratum is to accomplish the training with as little emotional stress as possible. Let it be simple and matter of fact. Rather than make it seem too important to the child, give it up, keep the home placid, and wait till the child wants help.

At level V is the highest cerebral complexity of integration. Here associations are somehow stored and conditioned, so that they are indi-



LEVEL V-SOCIAL, PERSONAL, EMOTIONAL

Common Lesions: None, or Hereditary

Clinical Results: Stammering, Stuttering, Anxiety, Psychoneurosis

Treatment: Ease Tension, Get Relaxation, Restore Confidence—suggestion, group work, accomplishment; Psychiatric talks, Psychoanalysis, Social Service

vidual, depend on past experience and when summed up constitute personality. The areas involved are shown in Fig. 5. These are the obverse of Fig. 4, which maps out all the specialized areas. What is left over is shaded in Fig. 5, and represents what one supposes, on fairly good evidence, to be the association areas, practically blank in infancy and loaded with personal experience in adulthood. These are the parts of the brain that permit the effect of one person upon another to register and effect character. This associative mechanism allows socialization to take place. When the environment is difficult it is this level of cerebral function that is first affected.

When put under unusual emotional stress, almost anyone stammers. Stammerers are people who habitually hesitate and stick in their speech under stress, but who can talk or read with little hesitation when alone and relaxed. The trouble does not seem to be with the organs of speech, they function well enough when the patient is alone; the essential trouble seems to be in the patient's social relations. He is "shy," cannot "put it over," is afraid to meet people, has varied anxieties and especially has become fearful that he will stammer if called on to speak. Certain sounds are especially difficult, but these vary from month to month and year to year, so it is probable that fear of a certain letter is the cause of the sticking, rather than the sound-formation itself. Any spring board

to start the speech and keep it going, like talking in unison or singing, will get rid of the stammer. Putting the patient on the spot by asking him a direct specific question will bring out the blocking in the speech.

For all these reasons stammering is thought to be a psychoneurosis and there is no doubt of the importance of neurosis as one of the causa-

For all these reasons stammering is thought to be a psychoneurosis and there is no doubt of the importance of neurosis as one of the causative agents. Everybody probably has stammered at times. It is the child who connects a *fear* that he will stick next time he tries to speak, who perpetuates the stammering into an anxiety state that may last for years. More complicated neurotic mechanisms are usually behind the fear about speech; the child is neurotically anxious and uses speech as the symptom rather than vomiting, bed-wetting, food fussiness or one of the many other possible neurotic expressions.

Experience in treating stammerers has shown that working on the neurosis and paying no attention to the speech will sometimes cure the stammering. Certainly the results of this procedure are better than giving lessons in elocution, breathing, etc. (which almost always make the patient worse) and better than the trick training methods of some of the stammering schools. The tricks of speech learned often help at first because they are taught with much positive suggestion and confidence is gained by the patient.

Probably the best methods are those that combine psychotherapy, socialization and speech exercise. Blanton⁸ has written a good book on this subject. Successful schools that do this well are run by Dr. Green in New York and Mr. Martin at Bristol, R. I. The patients must learn to relax, to speak without spasm, to literally "take it easy." Nothing helps this more than good suggestions, properly and repeatedly employed, and success. The success is the most important thing, it allays fear and builds confidence. Speaking in unison, singing, helping each other, all help the patient to extravert himself and shed his anxiety.

Sometimes one line of treatment alone will effect a cure. Jacobson⁹ in Chicago has had success with relaxation exercises alone. A few instances are known where psychoanalysis worked. Hypnosis has cured a few. But these phenomena must be looked at as examples of taking a few straws from the camel's back. If one wants to be sure to help, it is far better to use several methods of attack at the same time—directed against the fear, the spasm, and the social withdrawal. Inheritance is an important causal factor but nothing can be done about it. For the patient it is best forgotten; for the therapist, it should be constantly kept

mind. Most stammerers probably inherit an inferior speech apparatus (often linked with a left-handed or ambidextrous tendency). This may be harmless unless the social situation and the patient's interpersonal relations precipitate anxiety and fix it into psychoneurosis. The neurosis takes hold of the least resistant system and causes symptoms. The etiology is multiple, and treatment must be varied to match it. The inheritance of a weak speech mechanism is no obligation to stammer. Emphasis in treatment should be put on amelioration not cure, for few are ever entirely relieved of symptoms.

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THE PREVENTION AND TREATMENT OF CONVULSIVE DISORDERS*

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T is subject for our discussion tonight has for a score of centuries been the picnic-ground for a merry-go-round of inconclusive thinking. The twenty-seven different names which have been applied to convulsions and their contradictory connotations are evidence for this statement.

The "Sacred Disease" is opposed by the "Demon Disease"; the "Shining Disease" by the "Black Disease"; "St. Anthony Disease" by the "Filthy Disease." However, non-committal descriptive terms have survived longest, "Committalis Morbus," "The Falling Sickness," "Epilepsy" and our English, "Fits."

"Paroxysmal Convulsive Disorders," the choice of the American Neurological Association and hence, out of courtesy, my title for this evening, represents an effort to escape the fear and loathing which has encrusted the term "epilepsy" in its passage through the Dark Ages. The effort is commendable but the choice defeats its own purpose. "Convulsive Disorders" centers attention on the convulsion, the most fearful aspect of a seizure. "Disorders of Consciousness" would be a preferable term for two reasons. First, loss or impairment of consciousness is less feared than a convulsion; syncope is commonplace; sleep is an every day, or every night, occurrence. Second, and more important, loss of consciousness is the central sun of the constellation of symptoms which make up a seizure. The seizure most distinctive of epilepsy, both clinically and electrically, is the petit mal, a transient loss of consciousness accompanied by the three-per-second alternate dart-and-dome dysrhythmia. This form of seizure is relatively more common in so-called "essential epilepsy," is not reproducible by artificial means, such as the use of convulsant drugs, and constitutes abou 70 per cent of all seizures. Both consideration for patients and scientific accuracy vote for the

^{*} Read October 23, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

term "disorders of consciousness." Objection that there are many forms of unconsciousness can be countered by mention of the many conditions in which involuntary convulsive muscular movements are the presenting symptom—chorea, tetany, habit spasms, eclampsia, hiccup, sneezing, orgasm, and so forth.

Tempering the wind to the shorn lamb is an act of mercy and the physician in speaking to his patient often finds use for wishful words which also conceal: spasmophilia, pyknolepsy, fainting spells, or nervous turns. If we wish to go the whole way in both camouflage and scientific accuracy, the proper expression is "symptomatic cerebral dysrhythmia." However, sugar-coating is neither desirable nor necessary in this medical presence and with your permission, I shall substitute the unpleasantly familiar term "epilepsy" for the multiform "convulsive disorders."

Traditionally, etiological factors have been separated into two distinct groups. First is the so-called "idiopathic" or "cryptogenic epilepsy," seizures out of the nowhere into the here. The word "idiopathic" means "one's own suffering"-a condition, the cause of which is not extrinsic but arises out of one's own peculiar make-up, an inborn characteristic. The terms "idiopathic," "constitutional," and "hereditary" would seem to be interchangeable. In the second group, symptomatic epilepsy, seizures are the result of some pathology of body or brain. The last five years have altered 500-year-old conceptions. Idiopathic epilepsy is no longer a Jovian thunderbolt out of the blue, unpredictable and inscrutable, but is a disturbance in the chemical makeup or reactions of the discharging cells of the brain. This chemical disorder results in a disturbance in the orderly pulsations of the electrical currents of the brain and these electrical pulsations as recorded seem to be a hereditary trait. Studies of the brain-wave records of the epileptic and his relatives bring support to the suggestion that an underlying defect has been transmitted. Epilepsy is a double-headed dragon, but with only one heart, cerebral dysrhythmia, a heart which a daring Saint George M.D. will someday pierce. Instead of the obscure ancient terms "idiopathic" and "symptomatic," I propose the clear-cut terms "genetic" and "acquired."

This terminology has the advantage of placing epilepsy on the same footing as other metabolic diseases. The word "idiopathic" or "cryptogenic" implies an origin which is mysterious, and unknowable, a sort of

spontaneous combustion of devastating symptoms. "Genetic" implies predisposition or more specifically genes and chromosomes and their chemical structures which, if they cannot be seen, can at least be visualized. "Acquired" is entirely distinct from "genetic" and yet the processes are complementary. Modern geneticists emphasize what clinicians have postulated for centuries, namely, that heredity and environment are complementary factors whose joint action produce many of the ills which beset body and brain. Diabetes, hypertension, tuberculosis, obesity, cancer are but examples of scores of disease conditions which are both transmitted and acquired. Seed and soil combine to make a plant; spark and gunpowder, to make an explosion. Although in the great majority of patients both factors are at work, their relative importance varies from patient to patient. Probably the case is rare in which only heredity or only an acquired cause is responsible for seizures. Nevertheless, these two categories are clinically useful, if, when we speak of either genetic or acquired epilepsy, we recognize the probability that acquired or genetic factors respectively are also partially responsible. I stress this point because a comprehensive and effective program of treatment must be based on a recognition of multiple causes in the individual patient.

Prevention: If, as a general rule, "an ounce of prevention is worth a pound of cure," then in epilepsy a milligram of prevention would be worth a kilogram of cure. During the last twenty years I have examined thousands of articles which dealt with the subject of epilepsy but remember only a few which attacked the important subject of prevention. This neglect is due to the fact that a seizure is almost always a complete surprise to all concerned. "We never dreamed," say the parents, "that such a thing could happen to our child." Eighty-three per cent will add, "There has never been a case like this on either side." The doctor examines the patient, pronounces him sound and healthy, and mutters to himself. "Cryptogenic"—born of secrecy—"epilepsy." Having no conception of a cause, he cannot conceive prevention, though he may be able to provide symptomatic treatment.

As I have stated, there are two general causes of seizures, genetic and acquired, and in any given patient the twin influences are at work. However, in three fourths of patients, the genetic forces seem to prevail, and in one-fourth, one or more of the environmental factors. In spite of this preponderance, geneticists warn that even if sterilization of

epileptics were universally applied, benefit to future generations would be negligible, because the vastly more numerous "carriers" transmit the disorder as readily as epileptics but cannot be identified. We are able to stress prevention by means of eugenics only because of the almost telepathic aid given by the electroencephalogram.

This is not the occasion for a presentation of laboratory data but I need to say that Dr. and Mrs. Gibbs and I have made and classified electroencephalograms of 1,000 normal control persons, 1,260 epileptics, 320 near relatives of epileptics, and 80 twins (160 co-twins), identical and non-identical, epileptic and non-epileptic. 2,3,4 Study of these data leads to these conclusions: the pattern of brain waves is an hereditary trait; epilepsy, per se, is not inherited, but a predisposition is, and in most persons this predisposition, if present, is represented as an abnormality in the electroenchephalogram. The brain-wave pattern is not fixed but a fluid trait and various considerations blunt the sharpness of the deductions which can be drawn from it. Nevertheless, this technique seems to make it possible to trace the underground asymptomatic course of epilepsy through the generations, to give advice about marriage and childbearing based on individual rather than on general facts and possibly to take the offensive against epilepsy by starting treatment before the seizures begin.

Thus, the prevention of epilepsy by means of eugenics, requires the dying out or the breeding out of hereditary dysrhythmia. The question of whether transmitted dysrhythmia is a dominant or a recessive, and whether disordered brain waves could be "bred out" by crossing with ordered brain waves, must await the collection of more data and the decision of geneticists. Moreover, given a person whose electroencephalogram is abnormal, we must know that his dysrhythmia is transmitted and not acquired, and we must learn the genetic significance of various degrees and types of abnormality. It would now seem that epilepsy will be the chief beneficiary of this study, for of all neuropsychiatric disorders, dysrhythmia seems to be most consistently present (85 to 90 per cent) in persons subject to seizures. In epileptics the most distinctive abnormality is the intermittent appearance on the electroencephalographic record of short bursts of high-voltage waves which may be abnormally fast, slow, or else alternately fast or slow-what the Gibbs call "seizure-discharges." Records with this type of disturbance are found 33 times more frequently in epileptics and 7.7 times

more frequently in their relatives than in a control population. The corresponding multiples for records without seizure-discharges, but which are grossly slow or fast, are 19 times and 4.8 times. The multiples for records which are only moderately slow or fast are 2.3 and 2.9 times. Pushing the comparison still farther, in epileptics paroxysmal discharges are 13 times more important than moderate slowness or fastness of rate, and in the relatives of epileptics, they are three times more important. The proportion of petit mal patients in the group is influential in studies of this sort, for 86 per cent of patients who have only petit mal have records classed as paroxysmal against 45 per cent of patients who have only psychomotor seizures, and 17 per cent of patients who have only grand mal.²

Hereditary dysrhythmia can be prevented only by means of eugenics, either by forbidding progeny to all persons with transmitted and serious brain-wave disorders—an imposing task—or perhaps by dilution of the trait through their marriage with persons possessed of normal brain waves. On the other hand, even if a disordered pattern of brain waves has been inherited, epilepsy itself may possibly be prevented if environmental conditions which act as precipitants of seizures can be avoided. I refer to trauma received at birth or later in life from traffic or industrial accidents or from wounds received in war, certain infections which invade the brain or meninges, encephalitis, meningitis, whooping-cough, and syphilis, certain severe circulatory or emotional disturbances, and many convulsant drugs, the most common of which is alcohol. Prevention of these precipitating conditions lies partly with the public and its elected representatives and partly with the individual.

Finally, whether an observed dysrhythmia is transmitted or acquired there is the possibility of preventing the appearance of clinical manifestations through the use of anticonvulsant drugs in the pre-seizure period. This possibility has not as yet been tested. Obviously, it would be more apropos in children, in persons with definite seizure-discharges, and in those who have a previous history of brain injury or have displayed symptoms which might be premonitory—an infantile convulsion, temper tantrums, enuresis, periods of unexplained sleep, dizziness, falling, head-nodding, and so forth. Without the aid of the electroencephalogram, preventive measures must deal with such relatively indirect matters as better obstetrics, fewer wars, and a clearer recognition of premonitory symptoms.

Treatment: Insofar as treatment is based on etiology, the search for the cause or causes of seizures must be highly individualized. This requires careful history-taking and painstaking examinations. One must attempt to rule out each of the dozens of conditions which, if present, act as contributing causes for convulsions. Most prominent of these conditions are congenital maldevelopments, birth or later brain trauma, brain or meningeal infections, intracranial tumors, circulatory lesions, severe metabolic or endocrine abnormalities, toxemias, convulsant drugs, and borderline states simulating epilepsy. These latter embrace syncope, irritable carotid sinus, vasovagal seizures, hysteria, and eclampsia. A shrewd guess as to the presence or absence of one of these conditions can be made on the basis of a careful history and physical and neurological examination; in other words, at an office visit. However, the unexpected happens often enough to justify certain laboratory examinations as a routine. These include Roentgen-rays of the skull, urine and blood examinations, morphological and chemical, and in early cases, or in patients with localized symptoms, spinal fluid examination and possibly a pneumoencephalogram. În our experience, most important of the methods of examination is the recording of the electrical activity of the brain of the patient, and of his parents or other near relatives. These records give some idea of the relative importance of genetic and acquired causes, and of the type, severity, and localization of the disorder.

Corrective treatment is based on the elimination of abnormalities which seem to have a direct responsibility for seizures. The chief of these are tumors or scars of the brain which can be removed by the neurosurgeon, a task requiring the best of skill and judgment.

However, the activity of the brain is indirectly influenced by each body organ and cell and modern physicians do well to repeat some of the rules of health prescribed by Hippocrates. The maintenance of a healthy body and a confident mind, and participation in the work of the world is good medicine for all patients.

If, as happens in at least 95 per cent of patients, neurosurgery has nothing to offer, the physician has to rely chiefly on drug therapy. We preach the necessity of rational therapy, yet for these thousands of years the control of seizures has been empirical. Bromides and phenobarbital apparently act by virtue of their sedative action. They are general soothers of nervous activity and not correctives of the specific disorder of epilepsy. Dilantin sodium, on the other hand, seems to be of specific

value in certain types of epilepsy. Whether it improves the abnormal chemistry of neuronal cells which causes their disorderly and excessive discharge is a subject for future research.

Dilantin sodium was not stumbled on by accident but was the result of planned and patient search. I am sure 1 express the feelings of tens of thousands when I praise the Chairman of the Fortnight Committee, Dr. Tracy J. Putnam. He, it was who refused to believe that the chance discoveries of Locock and Hauptman could not be improved on by conscientious search. He, with Dr. H. H. Merritt, initiated the studies which led to the demonstration of the superior effectiveness of this non-sedative drug over the previously used sedatives. Dilantin sodium is the drug of choice for most patients subject to seizures. Epilepsy is a tough disease. Dilantin is a sharp weapon which must be wielded skillfully. In the beginning the physician must see the patient at frequent intervals in order to steer him safely between the rocks of toxicity and the whirlpool of continued seizures. The guiding principle is to increase the dose of Dilantin by gradual steps until a maximum therapeutic result is achieved or until symptoms of toxicity appear. The use of Dilantin sodium (phenytoin sodium), as explained in detail by Merritt and Putnam⁵ and others⁶ need not be repeated here. The matter of dosage requires reiteration. Many physicians who think of phenobarbital and phenytoin sodium in the same quantitative terms, have patients who say, "Dilantin does not seem to work with me." For most patients, the dosage of Dilantin should at least double that of phenobarbital, from 41/2 to 9 grains (0.3 to 0.6 gm.) a day.

Pleased as we are with finding this better weapon in our hands, the electroencephalograph warns against undue optimism. Improvement of brain waves usually lags far behind reduction in the number of seizures. Petit mal (dart-and-dome dysrhythmias) are often made worse by Dilantin. The problem of epilepsy will not be solved until cortical dysrhythmia can be controlled.

In addition to drugs, the physician should make use of social and psychological therapy. In my experience, the lot of almost every patient can be improved by attention to these domains. Not only can the physician help his patient by encouragement in intellectual and vocational pursuits, by reorientation of the attitude and hopes of the patient and his family, but he can also do much to correct the present deplorable attitude of the general public. A sign of the times is the formation

of the Laymen's League Against Epilepsy, a national organization with the twin aims of public education and encouragement of research.⁷ Local groups are also being organized. Large potentialities for good lie in the New York Society of Convulsive Disorders.

Problems of War and Epilepsy: Our thinking at present revolves around the means for survival in a world convulsed with war. Immediate medical problems are two. First is the duty of keeping epileptics out of the armed forces. The wisdom of this rigid policy may be questioned on the grounds that specially chosen patients when geared to special jobs might be outstandingly useful. In addition, there is the long-standing warning of geneticists that subjecting only the most fit to death and destruction is slow national suicide. Second is the problem of assimilating epileptics into industries which are suddenly labor-hungry. For the person subject to seizures, these two problems are cumulative. A history of seizures automatically throws the draftee into the bottom drawer of the discarded, a drawer marked 4-F. This procedure, in turn, automatically spoils his chances for work. "If the Army doctors say his physical condition is hopeless," reasons the employer, "I don't want him."

A further barrier to employment which operates in peace, as well as in war times, is the fear of the employer that he may be held responsible for any injury which the epileptic might sustain as a result of a fit "on the job." We have circularized the various states in the Union, asking about compensation codes as they affect the epileptic who may be injured while at work. Replies received from thirty-eight states indicate a lack of any uniformity in the laws or their interpretation. Of court decisions made in five of the states, two ruled that the company was liable even though a seizure caused the fall and the death. "A workman carries with him all his disabilities." At first glance, decisions which provide compensation to the epileptic whatever the circumstances would seem favorable to him. Practically, such decisions are disadvantageous. Because of them, or because of uncertainty in regard to liability, most employers will not knowingly hire an epileptic. It would seem only just that the epileptic should be permitted to waive his rights to compensation when injury results from a spontaneous seizure while at work. In only seven states does there seem to be a provision that an employee may reject the Compensation Act.

Even broader barriers to securing employment are the fear and horror which the sight of a convulsion produces in fellow employees,

the conception of an epileptic as a deteriorated, cantankerous or physically ineffective person who would not be worth his wages, and ignorance of the fact that new methods of diagnosis and treatment are now available. To gather information on the employment record of epileptics we have analyzed the histories of about 1,000 adult clinic and private patients, many of these furnished by colleagues throughout the country. Except for the temporary effects of disuse, the bodily machine of the epileptic is as sound as the average of the population. Not more than 10 or 15 per cent had disturbances of muscular power, coördination, or of control which would prove a serious handicap in physical work. Two-thirds of these patients were judged to be mentally normal by the examining neurologist. Of 608 men who answered the question about their ability to work, 54 per cent were fully able, 24 per cent were partially able, and 22 per cent were unable to work, for the most part because of seizures. Of the 407 women the corresponding percentages were 48 per cent, 34 per cent, and 18 per cent. Of 571 men who answered the question about employment, 97 per cent had formerly been employed, but only 73 per cent had a position when seen by the examining neurologist. Of the 410 males who were employed at the time of examination, 11 per cent were in a profession, 30 per cent in business, 22 per v skilled and 37 per cent in unskilled labor. The various occupations were distributed widely over the field of possible occupations.8

The adult epileptics in the United States when projected on the number of persons "gainfully employed" form an army of approximately 350,000 persons. A considerable proportion of this force, perhaps a quarter or a third, are unfit for productive activity. Too many of the remaining quarter million persons are denied a share in the work of the world because of public neglect, ignorance and prejudice. Physicians who prescribe inactivity for their patients, who do not know and practice recently acquired facts, who do not join in the campaign against epilepsy, must share the blame.

After the war is over both the relative and the absolute numbers of epileptics will be greatly increased. None will be killed in service but judging from the last war, from 5 to 15 per cent of the brain-wounded will become epileptic. The proportion may be greater now because chemotherapy will save the lives of men with serious brain wounds who before would have died. The hope of decreasing the burden of trau-

matic epilepsy lies with neurosurgery and with the finding of yet more effective anticonvulsant drugs.

Conclusions

In the light of new knowledge gained through use of the electro-encephalograph, the term "genetic" is suggested as a substitute for "essential," "idiopathic," or "cryptogenic" epilepsy, and the term "acquired" for "symptomatic" epilepsy. Efforts to prevent epilepsy are more feasible now than formerly. The principal agencies are: (1) the prevention of cerebral dysrhythmia, rather than of epilepsy itself, by means of eugenics; (2) the prevention of acquired conditions which act as a precipitant of seizures, and (3) possibly the treatment of persons who have either hereditary or acquired dysrhythmia in the pre-seizure period.

The important aspects of treatment are removal of acquired causes, the improvement of general physique, the use of anticonvulsant drugs, especially phenytoin sodium, and efforts to strengthen the psychological and social underpinnings of the patient.

War increases both the relative and absolute numbers of epileptics and makes it harder for those rejected by the draft to secure employment. In spite of the needs of industry, now labor-hungry, and in spite of the quarter million epileptics who are physically and mentally able to work, many thousands of persons are refused employment because of popular misinformation and prejudice, and because of compensation laws which may make the employer responsible for injury suffered as a result of a seizure. The efforts of clinicians, investigators and coöperating laymen should be intensified in and after this war period.

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SOME MEDICAL PROBLEMS OF VESICANT CHEMICAL WARFARE AGENTS AS AFFECTING CIVILIAN POPULATIONS*

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highly efficient under certain circumstances. Whenever it is necessary to use them against civilian populations, these will be used, especially when the danger of retaliation is not feared. There should be no overemphasis of the danger of chemical warfare against civilians neither should there be a complete denial of the possibilities of their use. If chemical warfare agents, especially the vesicants, are employed against civilians, they will be projected from airplanes in the form of sprays or bombs, or they will be used in varied sabotage techniques. Because of a fear complex of this phase of warfare, without actually using such compounds, the enemy can accomplish a great deal by merely suggesting that they might be used. European and Japanese peoples have had long training programs in chemical warfare defense.

Because of many obvious factors, chemical warfare defense training as regards civilians in this country is still in its early infancy. Fortunately, our army possesses excellent gas discipline and the Chemical Warfare Service is keenly alive to its present responsibilities in all phases of chemical warfare. At present, chemical warfare has not been used against civilians so that all civilian training must be done by theoretical principles. It should be added that for the civilian populace less disciplined and less well organized than the army, training for defense against chemicals is exceedingly difficult. Civilian physicians are very important parts of this defense scheme. They must first learn and receive training themselves before becoming part of the program. New York State was

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the first to develop, for the physician, a definite teaching program in the medical aspects of chemical warfare.¹

The highly effective chemical warfare agents, known as vesicants, or blistering agents are responsible for most of the difficult problems of civilian defense. Mustard agent, a term preferred to "mustard gas," BB' dichloro-diethyl sulfide (Cl CH₂ CH₂)₂ S, has been known since 1854 and had been used extensively in the World War I and in the Italo-Ethiopian War.

Mustard was introduced in World War I to cause casualties even if the soldier was protected by a good gas mask. This agent is a clear oily substance when pure, brownish or blackish in color when used in the field. The odor is interpreted variously as that of garlic, mustard, or horseradish. The stains on the ground resemble those of a thin machine oil. Because of its low vapor pressure (0.11 mm at 20°C) mustard is remarkably persistent, remains where it is discharged for considerable periods of time especially in areas where ventilation is poor. Sparingly soluble in water, this material is soluble in fats, oils and also in the organic solvents. It is also soluble to some degree in rubber. Oilskins, cellophane materials, and the like resist penetration of mustard. To reduce the melting point, carbon tetrachloride (15 per cent) is used. Phosgene, the pulmonary irritant, may also be used as solvent. Mustard agent is an efficient material by virtue of its toxicity, persistency, and penetrability.

But with all this long history of actual use and in spite of some published reports to the contrary,^{2,3} little is known of the mechanism of its local action. There is no immediate sensation on cutaneous contact, even with heavy splashes. The agent penetrates the cutaneous barrier both through the epidermis and into glandular orifices of the skin surface. The degree and rate of penetration depend, of course, on such factors as the concentration maintained on the surface, the local character of the skin as regards kerato-hyalin mass and thickness of the epidermis, the number of gland appendages, etc. The solvent may aid cutaneous penetration. To demonstrate the toxicity of this chemical warfare agent, 0.005 milligrams per liter of air is the figure for vesicant concentration. Most of the agent which does not vaporize from the surface of the skin or which is not removed mechanically by absorbents, solvents, or detergents or which is not changed chemically, passes into the epidermis and derma. There it reacts locally after "intracellular ab-

sorption," and produces cellular destruction of varying intensity depending upon the concentration of the agent and somewhat on the sensitivity of the individual to the agent. The latent period varies usually from six to eight hours. Then, erythema, edema, vesiculation and perhaps necrosis, develop in order. Mustard is a strong eczematogenic agent and individuals who work with it for any length of time become sensitized easily. Various forms of maculo-papular, urticarial and vesicular reactions can then be produced by much weaker concentrations of the agent, and even by inhalation. There may be also focal reactions in sites of old, healed mustard lesions. These focal reactions in sites of old burns have been observed following inhalation of very weak concentrations of mustard agent with the skin covered completely. In sensitized individuals pompholyx-like eruptions have also been observed following inhalation or cutaneous contact distant from the hands. Hypersensitivity of viscera other than the skin has not been reported as yet. The negro is certainly less sensitive to vesicants just as he is certainly less sensitive to the poison ivy oleoresin. The published reports of E. K. Marshall, Jr. and his co-workers and various Italian investigators on work with the natives of Africa bear out this observation. In our work with a group of twelve negro patients, no vesicles could be produced with concentrations giving severe vesiculo-bullous reactions on a control group of white individuals. A vesicle was produced however on a dark skinned negro who had a contact dermatitis at the time the test was done. An attempt was made to sensitize three negroes by daily applications of mustard agent for three weeks. This was unsuccessful. No reasons are known definitely for this difference in sensitivity. This decreased sensitivity of the negro to the vesicants should be considered in the civilian defense plans. We have had negative results with passive-transfer tests in regard to mustard sensitivity. Some mustard may be carried unchanged to distant viscera and there produce the phenomenon of cellular destruction. More frequently, however, changes in distant viscera may occur following the local primary reaction of the vesicant or some complicating local factor such as infection. In a similar fashion any unprotected surface of the body will react to the vesicant. Such surfaces include the cornea and conjunctiva of the eye, the entire respiratory tract4 or, following ingestion, the gastroenteric tract.4 Such is a very general and brief outline of the picture of vesicant action. This is not an explanation of the mechanism of the action. It should be added that

these problems in regard to the mechanism of vesication have exposed our ignorance of many of the basic mechanisms of physiology of the skin chiefly as regards absorption and adsorption by the skin and also the mechanism of skin sensitizations, and even of rational cutaneous therapy based on physiologic and chemical principles.

The vesicle may continue to enlarge for several days. This change is important to remember in regard to local therapy. These changes are associated with severe pruritus which persists for some time and which provokes, through scratching, secondary eczematization and infection. Healing is prolonged unusually for an ordinary vesicular contact dermatitis. Here is one point where the analogy to poison ivy dermatitis does not hold. To some extent, this slow healing is due to the depth of the lesion produced, much deeper than the usual blister of a poison ivy dermatitis. Vascular damage is reported to be another cause of this apparently slow healing process. Secondary infection may ensue. There is some disagreement as to the frequency of secondary infection. We have seen only one instance of secondary infection from the cutaneous testing to mustard agent of a large number of physicians. Of course, under field conditions, chances for secondary infection of cutaneous lesions are more numerous. The patient with an extensive mustard agent dermatitis does not present the systemic picture of a thermal burn of the same degree, but rather the mild toxic state of a severe poison ivy dermatitis. However, more studies are needed on the systemic reactions from pure cutaneous contact.

Of more clinical importance is the irritation of the respiratory tract, first manifested by sneezing, hoarseness, aphonia and then by signs of pulmonary irritation, of the so-called first lines of pulmonary defense, the trachea and larger bronchi. Then, follows a secondary pneumonia of a mixed infection type. This pneumonia is chiefly responsible for the death of the individual "gassed" by mustard. In the last war the slight eye injury, with little or no corneal involvement, was the most frequent type found. At present, when airplane projection will be used, more cases of moderate to severe corneal and conjunctival damage will be found. Gastroenteric reactions will be more apt to occur from the ingestion of contaminated food or even of water where mustard, only slowly hydrolized by the water, will still be irritant. These gastroenteric reactions were noted especially in the animals of the Ethiopians in the Italo-Ethiopian war. Sequelae following mustardization will occur from

any viscera damaged but the frequency of complication, even of permanent eye and pulmonary damage, at least in World War I, was surprisingly small.⁵ Whether the incidence of such sequelae will continue to be low with civilians who have less gas discipline, less efficient protection and less strong physical and psychological make-ups than soldiers remains to be seen. Scarring pigmentation, and artefactal lesions, because of the pruritus, may follow the dermatitis.

Now, an individual protected by a gas mask and exposed to mustard agent, liquid or vapor, is not an immediate casualty. He is able to carry on his duties for some hours. Even then when lesions appear, he is uncomfortable but still able to do some work. Moreover, after a prolonged period of hospitalization he may return to active duty. In an effort to "correct" some of these deficiencies, another agent was developed by the Army at the end of the war. This was B chlorovinyldichlorarsine, lewisite, Cl CH: CH As Cl2, an arsenical compound. This material was first initiated at the American University and then elaborated on by Professor Lee Lewis of the Army Chemical Warfare Service. This compound was supposed to include many of the properties of the other agents used in chemical warfare. The appearance of the pure and "field" mixtures of lewisite is similar to that of mustard, but the vapor pressure of lewisite is only 0.4 mm at 20°C. This makes it less persistent than mustard. Its freezing point 5°C. (app.) is lower however than that of mustard, 14.4° C., so that lewisite mixtures are more apt to be used in colder climates. The odor of pure lewisite is pungent and irritant. Burning of the eyes and nose and tightness of the chest are symptoms produced by smelling pure lewisite. The odor of the product used in the field and the odor of material remaining on laboratory equipment is similar to that of geraniums. This odor may be due to decomposition products of lewisite. There is an immediate burning and pricking of the skin after lewisite contact, even from the vapor. The development of the vesicle is more rapid, twenty to thirty minutes, and the vesicle is much larger than the mustard vesicle and in its complete development presents no areola. However, this red areola does become marked during the latter stages of the development of the lesion. Although the cloudy fluid of the lewisite blister is supposed to contain arsenic, we have not been able to detect arsenic, with sensitive methods, by analyzing the contents of the twenty-four hour and older blister. In one instance, the cutaneous cap of the blister was included in the analysis. We have not

examined blisters less than twenty-four hours old. It has been our experience also that this blister fluid of the older blister, is not irritating to the adjacent skin nor to the skin of other individuals. This material was applied to other individuals by the patch test technique. Stains for arsenic crystals with the sulphide and bismuth-sulphide techniques reveal, in man, crystals of arsenic salts scattered deeply in the derma and beyond the confines of the visible inflammatory process. Keller⁶ in his series of one hundred patients, found no secondary infection of the lewisite vesicle in spite of its purulent contents. We have cultured the contents of the four and five day old lewisite blister in ten patients. In one patient gram positive cocci were found on direct smear and also on culture. The patient had a concomitant staphylococcal ecthyma. In another patient gram positive cocci were found only on culture, not on direct smear. It was assumed that this culture was from contamination.

Keller worked with mustard and lewisite in benzol and tested white individuals, by the drop method, on the exposed skin of the back. He reported that in spite of the higher concentrations of lewisite which he used, this agent caused weaker reactions on the skin than the mustard. He did admit, however, that the threshold dose varies widely with individual sensitivity. Arsenical poisoning results from lewisite contact and the intensity of systemic poisoning varies with the amount of arsenic absorbed by the tissues. Pulmonary edema in animals may be produced by cutaneous contact. Bile duct necrosis, without liver drainage, has also been mentioned in animals following application of the lewisite to the skin.7 As with mustard, similar and perhaps more severe irritations of the eye and respiratory tract may follow contact with lewisite. Another arsenical vesicant agent more important in the military situation than in the civilian area is the less persistent ethyldichlorarsine, C2H3 As Cl2. In some of the casualties from this agent in World War I paronychiae were reported. This is less effective than lewisite. Many other compounds have been examined and continue to be examined for vesicant action. For the civilian, however, mustard and lewisite should be his chief concerns.

A very important use of these agents in regard to civilian populations is their role in sabotage. It is scarcely practical to contaminate large water supplies by mustard or lewisite. But small unprotected water supplies can be poisoned. Undissolved mustard may remain for several

weeks at the bottom, the soluble portion slowly hydrolized. (Cl CH₂ CH₂)₂ S+2HOH→2HCl+(CH₂ OH CH₂)₂S

(CH2 OH CH2)2S is thiodiglycol and is non-toxic. The Army considers contamination of water more than 500 p.p.m. of mustard as unfit for drinking purposes. Boiling will render water safe. With the arsenical agents, soluble arsenious oxides can not be removed by ordinary water purification processes. Lewisite is hydrolized rapidly by water, and the chlorovinylarsenious oxide formed is relatively unsoluble but is still a vesicant, less active however, than lewisite.

Cl CH: CH As Cl₂+HOH→Cl CH: CH As O+2HCl

"If the arsenic content does not exceed one to five p.p.m. the water would be safe to use for periods varying from one day for higher concentrations, to one week for lower concentration. If larger quantities of arsenic are found, or if other non-contaminated supplies are available, the water should be pumped to waste."8

The vesicant agents also lend themselves for sabotage purposes in the industrial plant. Since mustard and lewisite are both soluble in oils, contamination of all machine oils by these agents is possible and then the machine itself can become dangerous for the workmen to touch and perhaps, difficult to decontaminate. Machine tools may be contaminated deliberately with vesicants so that the unsuspecting workman may get severe irritations of the skin from contact with these tools. Warehouses, especially food depots, may be sabotaged by mustard and lewisite. Expert advice will have to be secured in order to determine the extent of contamination and proper technique of decontamination of the foods. Shipping areas may be sabotaged by mustard and lewisite, by means of land mines, and these areas will be dangerous until decontaminated. Sometimes, the only thing necessary to produce panic is to suggest that chemical warfare agents may have been used or to use harmless materials with odors of mustard or lewisite and valuable working time will be lost until detection services and trained technical gas officers disprove the rumor.

It is possible, of course, to diagnose contamination of an individual before clinical signs ensue. This may be done by the history of exposure which includes degree of protection and the extent of personal decontamination, the appearance of stains on clothing and skin, the odor of the casualty, and the use of detector papers which change color on contact with the agents. Most of these detector papers at present require

fairly high concentrations of agent to affect a color change. For practical purposes, however, it is sufficient to diagnose simply vesicant contamination since the details of prophylaxis are really not specific enough under field conditions, nor do they warrant time lost in attempting a differential diagnosis.

The Medical Division of the Office of Civilian Defense has given adequate instructions^{9,10,11,12,13,14} in regard to protecting individuals from chemical warfare agents. It is important to know and to teach these official recommendations since decontamination of a potential casualty can be done most promptly and therefore most effectively by the individual himself. To do this he must be trained correctly. The individual, at present should not be taught to rely on chance evacuation to an established medical unit nor to make too many demands on official personnel, such as Air Raid Wardens, during and shortly after raids. For those civilians required to be outside during a chemical warfare attack, adequate protection from vesicants will be obtained. A basic knowledge of these agents will aid individuals in the improvisation of equipment for surprise attacks or for unprotected groups. Many types of improvised masks have been suggested but not too much reliance should be placed in these, unless they have been made with great care and have been approved by the Office of Civilian Defense or by the Army Chemical Warfare Service. A false sense of security may be given and since many of these agents have insidious actions, the inefficiencies will not be detected until it is too late. The heavy handkerchief soaked in baking soda solution or sodium hypochlorite solution is just as effective for brief periods. With vesicants, the eyes must be protected by attempting to keep them closed if possible and not rubbing them, or by some sort of close fitting cellophane or plastic goggles or industrial goggle or even underwater goggles. Bathing caps, hats and umbrellas will protect head and scalp especially from aircraft spray. This is important because adequate decontamination of hair is difficult. To protect the body, any type of impermeable material may be used. These include, of course, such materials as raincoats, cellophane (heavy laminated types), aprons and sleevlets, oil cloths, shower curtains, etc. Heavy rubber gloves will protect the hands and heavy rubber boots or galoshes will protect the feet. We have had the opportunity to observe an individual who suffered vesicular lesions on the foot from mustard which penetrated through the shoe. After an accident in the laboratory the shoes and clothes were inspected carefully and pronounced free of contamination. The individual was examined some hours later again. Yet, some fourteen hours after the accident, a diffuse erythema appeared over the dorsum of the toes of the right foot. This was associated with severe pruritus. Later, two small vesicular lesions developed. The shoe was discarded.

The official gas masks and complete anti-gas clothing either of the oil-skin type or of the impregnated type, cotton clothing impregnated with special solutions of the Army Chemical Warfare Service, constitute the official protective measures for the individual. Many medical problems arise in regards to these individual protective measures against vesicants. For the healthy individual the wearing of a gas mask produces no significant changes in his cardiovascular and respiratory dynamics. There are the questions of special masks for infants and children, for invalids with chronic cardiovascular and pulmonary conditions, of special masks for head injury cases, etc. Of course, the obvious answer to these questions would be evacuation in advance of such individuals. Moreover, if clothing is impervious to the passage of the vesicants, likewise it is impervious to the passage of air. In such outfits, heat loss of body is seriously interfered with since there is little opportunity for heat loss by physical factors such as the evaporation of sweat and radiation. When one attempts to do some degree of exercise in these suits the limits of tolerance are reached very quickly. Splashing the suit with cold water has been tried to lower the temperature of the outfit. In hot weather the usual limit is about thirty minutes before heat stroke may ensue. Strong individuals should be chosen for those units, such as decontamination squads, required to work in such suits. Cotton suits impregnated may be worn for longer periods of time but these suits do not protect against heavy splashes of liquid vesicants on their surface.

Because of the rapid absorption of the vesicants by the skin and by the eye, ideal prophylactic therapy must be done as rapidly as possible. For liquid splashes on the skin and for eye contamination, prophylaxis must be done at once. After about five minutes of liquid contamination of the skin, prophylaxis is not effective. If one waits until a medical installation is reached it may be too late to prevent any lesions. Therefore, it is important that the concept of personal decontamination be emphasized for individuals with partial or complete lack of protection against vesicants. The mechanisms of surface decontamination include

absorption, adsorption, hydrolysis and oxidation. The details of these processes are given in official publications of the Medical Division of the Office of Civilian Defense. There is some confusion in regard to recommendations as to the uses of solvents. With careful technique, gentle blotting from the periphery of the contaminated spot to the center, the organic solvents in which mustard or lewisite are soluble, may remove an appreciable amount of unabsorbed agent from the skin surfaces and from the gland orifices. If solvent is used too carelessly or rubbed too vigorously, it may actually favor absorption of agent into the skin. Work continues to be done on the forms of oxidizing agents to destroy or to render less soluble or less toxic any vesicant agent remaining on the skin. It is extremely doubtful whether these oxidizing agents can affect agents absorbed into the skin. The oldest and most active oxidizing agent forementioned is bleaching powder which reacts with mustard to form dichloroethyl sulfoxide.

 $(Cl CH_2 CH_2)_2S+Ca O Cl_2\rightarrow (Cl CH_2 CH_2)_2 S=O+Ca Cl_2$ With some oxidizing agents, under certain conditions, the sulfone may be formed. The bleaching powder will oxidize lewisite also. Relatively little bleaching powder will be available for civilian use at present. Possibly its best substitute at present for the use on streets, buildings, apparatus, etc. is the dual injector decontamination unit apparatus of lime slurry and chlorine gas.¹⁰ The chlorine content of this mixture is low however. Because of its highly irritant properties bleach has little use in skin decontamination save where it can be removed quickly.15 When no other materials are available, bleach mixture may be used for general sponging of the body; this mixture should contain four grams of bleach powder to five hundred millitres of water. In the civilian protection scheme, household buffered sodium hypochlorite mixtures, containing about 5 per cent of sodium hypochlorite will be available for decontamination of the hair and skin. 16 The Protective Cream of the Army Chemical Warfare Service is excellent protection against mustard and even against lewisite. For lewisite this Protective Cream offers protection only when the cream is on the skin before lewisite contact. With regard to lewisite the peroxides are preferred at present as the decontamination agents.

These peroxides must be used within five minutes after contact with the agent. Hydrogen peroxide, zinc peroxide, benzoyl peroxide, urea peroxide, and sodium perborate, are some of the compounds used. If these compounds are used one must regard critically their oxygen activity and their stability. Unlike with mustard, water is possibly the best practical prophylactic agent for lewisite since the hydrolysis is so rapid. The skin surface must be rinsed well afterwards. Splashes of vesicant on the skin are definite medical emergencies and fraction of minutes count. It is important to emphasize that eye contamination is also a definite medical emergency. In the eye, no oxidizing agents or strong solvents should be used since any corneal damage which these materials cause will make for deeper lesions by the vesicants. Correct gentle irrigations with saline or 2 per cent sodium bicarbonate solutions are recommended. There is some controversy at present as to whether irrigation should be continued when the eye lesions begin to develop. There are no good materials for instillations in the eye for prophylaxis before contact. Here, only the improvised or officially recommended mechanical devices for protection will be effective. Since tiny droplets from airplane spray are very dangerous to the eyes, individuals such as airplane spotters and the like should be protected in advance.

When the vesicant lesion develops there is no longer any question of so-called specific therapy. The materials recommended for prophylaxis can not be used here since these chemicals are too irritant for damaged tissues. There is need at present for substances which can function both as effective prophylactic agents and non-irritant therapeutic materials. With the development of the vesicle and bulla the local treatment^{17,18} is similar to that of a severe poison ivy dermatitis. It is only some hours, possibly not until the next day, after the chemical warfare attack that these lesions will appear and the casualty will become uncomfortable and then the rush to the casualty stations and hospitals begins. All efforts should be made to keep these lesions as clean as possible.¹⁹ Debridement should be done. For the small lesion under 0.5-1.0 cm. healing will occur no matter what form of local therapy is used. These treatments may include solutions of isoamyl salicylate, the conventional wet compresses of diluted alum subacetate, permanganate, etc. or the sulfadiazine suspensions, either in water emulsions types or in collodion, or with the crusting techniques of tannic acid-silver nitrate combinations. As for the larger lesions, it is well not to apply crusting

techniques too early since, unlike the bullae from thermal burns, the bullae from mustard and lewisite may continue to advance for forty-eight hours and the edge of the formed crust may not extend up to the edge of normal skin. Cold compresses help to relieve some of the severe pruritus ever present. Later, various anti-pruritic mixtures may be used. If nursing services are restricted, crusting techniques should be preferred. As with thermal burns, crusting techniques should not be used on the face, genitalia, hands and feet. It should be emphasized that the purposes of local therapy are to make the patient more comfortable, to prevent secondary eczematization and infection from scratching. Because of the systemic poisoning from lewisite contact, efforts should be made to remove or immobilize arsenic in the tissue adjacent to the contact site so that there will not be continued absorption from this area. Of course, the ideal method to accomplish that is by complete excision, but this is scarcely practical. Efforts to keep serum oozing from the lewisite area, injections of oxidizing agents (type?) into the contaminated tissues, peroxides locally on the area, ferric hydroxide pastes, have all been suggested as local therapeutic materials. The question of sulfa therapy for prophylaxis in extensive mustard or lewisite lesions has not been determined as yet. We have demonstrated sulfathiazole in the bullae of dermatitis herpetiformis. We have also demonstrated sulfa-compounds in the experimental mustard areas of animals.

Save for signs of arsenical poisonings with the arsenical vesicants and signs of pulmonary irritations in an unprotected individual, it is unusual to find any marked systemic reactions early in the course of even severe vesicant casualties. There is not much data available at present on protein balance or hemoconcentration in extensive vesicant cases. However, if plasma is indicated it should be given. When there are obvious signs of pulmonary irritation, cough, etc., in addition to the usual measures, sulfadiazine may be given as prophylaxis against the secondary bronchopneumonia which is almost certain to develop. For the arsenical poisoning such measures as repeated biliary draining, glucose, vitamins, etc. may be used. The treatment of eye injuries should be left to the ophthalmologist.

Those who preach the horror of chemical warfare forget the casualty figures of the past war.²⁰ In the American Army, of 70,752 casualties from gas only 1421 or 2 per cent died. Of these 70,752 gas casualties there were 27,711 casualties from mustard with 599 deaths or mor-

tality of a little over 2 per cent. With none of the horrible scars or deformities and with considerably lower incidence of blindness, chemical warfare is definitely easier on the casualty. There are no figures available as to the total mustard casualties of the Italo-Ethiopian War nor are there any figures available as to the casualties from the uses of lewisite mixtures by the Japanese against the Chinese.

Because of the long convalescence and the discomfort of the patient, all extensive cases should be hospital cases. The patients should be kept on bright, cheerful wards preferably under the care of dermatologists since these physicians are accustomed to treat such pruritic resistant dermatoses as result from mustard or lewisite. Complications such as one would suspect in similar types of cases may develop. For civilian groups individuals will be found to focus attention on their eyes, skin, respiratory tract or even cardiovascular system and to express psychoneurotic symptoms in these areas. Because of the undue fear of chemical warfare and because of overemphasis of complications, such psychoneurotic reactions should be expected to come frequently, if mass raids are made. The prevention of such reactions should be emphasized through all phases of the civilian protection scheme by repeated complete examinations, reassurance of absence of all findings, separation of such cases from convalescent vesicant cases. When the patient is discharged, it should be emphasized that no additional medical supervision is needed. Otherwise, compensation burdens for the community will be acquired for years to come.

The physician must realize that complex situations are suggested when methods of defense of civilian populations against chemical warfare are considered. The problem is more difficult when one realizes that all questions in regard to chemical warfare against civilians are on a purely theoretical basis at present. The difficulties of protection against the vesicants arise chiefly from the facts that these agents are toxic in minute quantities, can persist for long periods of time after discharge and that they can penetrate ordinary clothing and many building materials so effectively. First, the physician must educate himself.²¹ He is helped in this by the state educational programs in medical aspects of chemical warfare such as the state of New York has developed in each of its medical schools. Since the field of chemical warfare is of necessity a military one, newer developments will be made available only when possible. As much as he may detest and like to disregard them,

the physician must learn some details of organization because otherwise his theoretical plans of prophylaxis and therapy will not be able to be carried out. The physician will need considerable technical help,^{22,23} because the field of vesicant agents has so many technical problems referable to the detection of agents, the contamination of streets, buildings, food and water supplies, and the construction of special medical stations, with casualty stations and with hospitals, where chemical warfare cases can be handled with safety to the attending personnel and with justice to the patient himself. This technical help will be engineers, chemists, etc. who will be trained as non-medical gas officers. To prevent chemical warfare sabotage in large plants special plant gas officers will be trained. The evacuation of chemical warfare casualties from the first episode after emergency care for the casualty by the air raid warden, to the hospitalization of the severe case with complicating eye injury, pulmonary irritation, associated hemorrhage or shock, is an extremely complicated scheme. Each unit will have to work out its own evacuation procedures. Plans can be made and even extensive training problems can be adapted in the absence of equipment. Casualty figures in an area prepared and trained in advance will be low.

When the physician understands and learns the uses and limitations of chemical warfare, the principles of prevention and treatment, he will not be panic stricken upon the introduction of any new agents. If odors are absent or disguised, if combinations of agents are used, if other vesicants with other systemic effects are employed, the trained physician can still use the same principles which he has learned with mustard and lewisite as his training problem examples. Chemical warfare advances are definitely military secrets and in this total war the physician must learn to accept this. With his background in chemical warfare training he will adapt any new details easily and effectively when these details are furnished.

CONCLUSIONS

The vesicant agents, chiefly mustard and lewisite, because of their toxicity, persistency and penetrability are responsible for most of the complexities of the scheme for the defense of civilian populations against chemical warfare. The physician is a very important part of this defense scheme. He must secure special training in the medical aspects of chemical warfare to carry out his role. Such training programs are available

at present. Little is known of the theories of the action of vesicants. A great deal is known of their toxicology and pathology and of their specific prophylaxis. The treatment of the resulting lesion is purely symptomatic, namely that of a vesiculo-bullous, resistant and pruritic dermatosis with strong sensitizing properties. Mustard and lewisite dermatitis are not strange or mysterious maladies to the dermatologist. For those vesicants with systemic poisoning components, such as the arsenical compound, lewisite, therapy for this systemic phase should be given also. Decontamination of an individual will be done most effectively by the individual himself. The evacuation of the actual casualty must be done in a different mode from other warfare casualties since all cases contaminated by vesicants are dangerous to handle. In the technical phases of decontamination the physician will have the help of a trained non-medical gas officer and the industrial physician will have the help of his plant gas officer. The educational program of the physician must also include measures to prevent psychoneuroses which would be expected in large civilian groups. With his knowledge of the principles of prevention and therapy, the trained physician will be able to cope with any new agents which may be used. In all these ways, the physician will learn the real role of chemical warfare against civilians and will avoid acquiring for himself and consequently spreading by teaching. those factors of overemphasis, exaggerations, panic and fears, all reactions so earnestly desired by enemy propaganda services.

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general practice. [4. ed.] Chic., Year Book Publishers, [1942], 243 p.

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Strecker, E. A. Fundamentals of psychiatry. Phil., Lippincott, [1942], 201 p. INTERNATIONAL SOCIETY OF SURGERY REORGANIZED HEADQUARTERS TRANSFERRED FROM BELGIUM TO THE UNITED STATES*

By a vote of the delegates from all of the affiliated societies of the Americas, representing Argentina, Brazil, Canada, Cuba, Ecuador, Guatemala, Mexico, Paraguay, Peru, United States, Uruguay and Venezuela, the headquarters of the International Society of Surgery was provisionally transferred from its European headquarters in Brussels, Belgium, to the United States. More specifically, the headquarters has been established in the Inter America Division of The New York Academy of Medicine in New York City.

In explaining the need for the change in headquarters, Dr. Rudolph Matas of New Orleans, Acting Secretary and Treasurer of the International Society of Surgery said:

"The German occupation of Belgium and the Nazi devastation of the rest of Europe and all the other war-torn nations, had virtually restricted the international relations of the Society to the Western Hemisphere where its fellowship is widely spread through its affiliated branches in North, Central and South America.

"The Executive Committee of the United States Division, the largest, most active contributor to its transaction, felt it their duty conjointly with their Latin American colleagues to rescue the Society out of the perils of the European conflagration. The first steps were taken November 1941 at Boston but no final action could be taken to transfer the official sanctum in Brussels to America without the concurrence and approval of all the affiliated branches in America."

The act by which the transference of the International Society of Surgery from Europe to the United States was effected, was signed either personally or by proxy by the Delegates from all the affiliated societies of the Americas.

By the action of the Council of Delegates, the official seat of the Society will be established in the Inter-America Division of the New York Academy of Medicine, directed by Dr. Mahlon Ashford, where Dr. Enrique J. Cervantes, Assistant Secretary-Treasurer of the Executive Committee, Editor of "América Clínica," the official organ of the society and Editor and Secretary of the Hispanic-American Medical Society, will be able to render service to the Fellows of the Society and medical visitors hailing from the Latin American countries.

The affairs of the International Society of Surgery are to be administered by an Executive Committee composed of the following: Dr. Elliott C. Cutler, Col. M. C., U. S. Army, Chairman in Absentia, Dr. Eugene Pool, Dr. Arthur W. Allen and Dr. Rudolph Matas, Acting Secretary and Treasurer.

The meeting was presided over by Dr. Eugene Pool, who serves as Acting Chairman of the Executive Committee for the United States, in the absence of Colonel Elliott C. Cutler, now at the front.

Dr. José Arce, Dean of the University of Buenos Aires, will serve as Acting President of the International Society of Surgery in the absence of Professor L. Meyer of Brussels, detained in Belgium by Nazi compulsion.

The revision of the Constitution adopted on Thursday, November 12, 1942 was prepared by Dr. Rudolph Matas of New Orleans, former President of the Society and now Acting Secretary-Treasurer. A representative group of Fellows from New York and elsewhere signed the Act of reorganization, as witnesses of the signing of the Act by the delegates of the Governing Council, among whom were Drs. Walter Estell Lee of Philadelphia, Russell S. Fowler, Ralph Colp, Edwin G. Ramsdell, Frederick W. Bancroft, Howard Lillienthal, Charles Elsberg, Seward Erdman, Carl Eggers, Henry Lyle and others elsewhere, by proxy.

The establishment of an Inter-America Division of the New York Academy, with the opening of the editorial offices of "América Clínica," the most widely read of Spanish-Portuguese medical publications in South, Central America and Mexico and the opening of an Inter America Bureau to render a free service for medical information, has proved probably the most valuable of all the practical contributions that the United States has made to the cause of Latin American good will and friendship.

^{*} Contributed by Dr. Rudolph Matas, November 28, 1942.

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



FEBRUARY, 1943

GALL BLADDER DISEASE: ETIOLOGY, DIAGNOSIS AND TREATMENT*

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abnormalities frequently are seen to precede and serve as a basis upon which disease processes develop. Thus gall stones, cholecystitis, etc., are beginning to be looked upon as organic lesions developed upon an underlying disturbance in structure or function. With

This includes the following lectures:

R Franklin Carter "Modern Methods of Diagnosis in Disorders of Gall Bladder Based on Anatomy and Physiology" Presented on February 27, 1942 in the Friday Afternoon Lectures

Thomas H. Russell: "Indications for Surgery and the Surgical Treatment of Diseases of the Gall Bladder" Presented on March 6, 1942 in the Friday Afternoon Lectures

this knowledge has come the realization of the necessity of dealing with the basic disorder as well as the engrafted pathology, if a complete cure of the condition is to be effected. Such a concept is comparable to the more widely held views relating to diseases of other parts of the gastrointestinal tract, e.g., peptic ulcer and ulcerative colitis.

The concept of gall bladder disease expressed herein has been arrived at through the efforts of the members of a combined clinic for the study and treatment of gall bladder disease established at the New York Post-Graduate Hospital in 1929.* Grouping together the physiological chemist, pathologist and clinician for studies of disease processes casts a new light on previous concepts of management of disease of the liver and gall ducts. Further, the careful sifting of material collected by such a group leads to final conclusions based upon more rational concepts than those arrived at by individual impressions gained from the daily routine of private or individual hospital practice.

The new view does not necessarily change the previous pathological classifications. It adds a new phase, an early dysfunction stage. The failure to eliminate the basic functional disorder by those means directed only toward the engrafted disease complications is emphasized.

The clinic was established for the specific purpose of "determining which patients will be relieved of their symptoms by cholecystectomy." The clinic has been operated by representative members of the various departments. Full time and part time members have participated. Both medical and surgical problems in gall bladder disease have been subjected to a critical analysis under this combination which has been ably assisted by members of the laboratories in physiological chemistry, bacteriology, pathology, and roentgenology.

The classification of gall bladder disease, the mechanism upon which the disease is based, and the special diagnostic signs presented herein are the result of the analysis of the data accumulated in this clinic during the past thirteen years.

From an early study of the data one concept stood out prominently. Continued experience has emphasized and substantiated its importance. Today this concept stands foremost, viz., that gall bladder disease is progressive. Whatever the initiating process, be it functional or organic,

^{*} The clinic was opened under the medical directorship of Herman O. Mosenthal and continued through the directorships of Walter G. Lough and Irving S. Wright; under the surgical directorship of John F. Erdmann and continued through the directorships of Charles Gordon Heyd and Thomas H. Russell. J. Russell Twiss and Carl H. Greene have been the active directors in medicine and R. Franklin Carter the active director in surgery.

time adds factors such as gall bladder stones, infection, obstruction and obliteration of the gall bladder. Then the influence of the initiating factor often begins to exert its influence directly upon the common duct. Here again, the process may be either functional or organic, with the factors of common duct stones, infection, obstruction, cirrhosis of the liver and spleen occurring in the course of time.

The second fact realized, no less important than the first, was the necessity of determining the actual underlying cause of the disease process, i.e., the initiating factor. The importance of understanding the mechanism setting the disease process in motion lies in the fact that treatment of the organic lesion such as removal of gall bladder stones and even the gall bladder itself may not result in the complete eradication of the initiating factor. This will be seen in the section dealing with hypertonic dyssynergia. Cholecystectomy fails to relieve the patient's symptoms when the sphincter of Oddi is the actual site of the difficulty. The best explanation offered for the pre-operative pain in this type of gall bladder disorder is that the nerve endings in the wall of the gall bladder are excited by a pressure stimulus developed within the cavity. Two forces are at work; the resistance of the spastic sphincter of Oddi to the emptying of the gall bladder and the exertion of the gall bladder musculature to overcome this resistance. The opposition of these two forces results in an increase of tone in the gall bladder to the point of tonic contraction. Colic mechanisms of this nature are seen in other hollow viscera, e.g., urethral obstruction. Postoperatively the pain is due to the increased intraductal pressure resulting from the sphincter spasm. In contrast, cholecystectomy may be expected to cure the disease process when it is limited solely to the gall bladder itself, as will be shown in the section on anatomical causes disturbing the filling and emptying mechanism of the gall bladder.

Still another fact of importance was the necessity of determining pre-operatively the presence or absence of actual infection in the gall bladder. This will be discussed in the section dealing with infectious cholecystitis.

The general routine in use by the clinic is as follows: After a history and physical examination, a blood specimen is taken for the determination of cholesterol and cholesterol esters. The normal total cholesterol in the blood varies from 160 to 220 mgm. per cent. The esters range from 40 to 60 per cent of this total if liver function is normal. The icteric

index and Van den Bergh tests are also done. The cholesterol-ester ratio is not the sole liver function test used. In patients in whom liver function impairment is suspected, other recognized tests are also utilized, e.g., the cephalin flocculation test, bromsulphalein test, etc.

A duodenal drainage is then performed with sterile technique. Four specimens are obtained. First, a specimen of the gastric juice on which the total acidity and free hydrochloric acid are determined. When indicated, a fractional test of gastric secretion is performed. Next, a specimen of the duodenal contents is obtained before any type of stimulant has been administered. This is referred to as the "D" specimen. After this, one ounce of 25 per cent magnesium sulphate is introduced through the tube. The specimen obtained is referred to as the "M" specimen and is of a darker amber color than the "D." Lastly, one ounce of olive oil is introduced into the duodenum. This stimulates the gall bladder to contract, and under normal circumstances, dark concentrated bile, referred to as the "O" specimen, is obtained. The obtaining of specimens as described above constitutes a normal response to duodenal drainage. Variations from this pattern constitute an abnormal response, e.g., the failure to obtain concentrated bile after stimulation with olive oil in a patient who has an intact gall bladder. Patients who respond in a similar manner to several drainages are said to have a regular response. Those who differ from drainage to drainage, e.g., concentrated bile one time and not the next, etc. are said to have an irregular response. Each specimen of bile is examined microscopically for evidence of stasis, i.e., the presence of crystals, either cholesterol or calcium bilirubinate. Normally, no crystals should be found, or at the most, an occasional crystal per 10 low power fields. Specimens are sent for bacteriological culture, and under normal conditions, should be negative. In special cases, the pancreatic ferments in the bile specimens are determined. A roentgenogram series of the gall bladder is taken using a double dose of dye given orally.

Disease or dysfunction of the gall bladder and the biliary tract manifest themselves either in the history, liver function test, duodenal drainage, or roentgenogram. By integrating these findings, patients are classified into various etiological categories prior to initiation of therapy. If surgery is indicated, cultures are made of the operative specimens. A chemical analysis of the bile is also done. Thus, the pre-operative classi-

fication is checked by the operative findings.

ETIOLOGY (INITIATING FACTORS)

Patients may be divided into three groups:

- 1. Those with disorders resulting in a disturbance of the filling and emptying mechanism of the gall bladder.
- 2. Those with disorders resulting in interference with the concentrating mechanism of the gall bladder.
- 3. Those with diseases of the blood and metabolism which manifest themselves in disorders in the biliary tract.

In the ensuing discussion of the various etiological factors of gall bladder disease, it has been our aim to seek out the cause by which each factor produces its effect. Treatment is directed wherever possible at removing both the cause and effect. The prognosis in any group depends on the success of the available treatment in achieving this dual purpose. The particular clinical and laboratory findings pertaining to each group are mentioned. The consideration of each group in such a manner, enables the comparison of the various etiological factors as regards mechanism, treatment and prognosis.

DISORDERS AFFECTING FILLING AND EMPTYING MECHANISM

Disorders resulting in disturbances in the filling and emptying mechanism of the gall bladder are listed in Table I. The causes of these disturbances may be anatomical or physiological. The anatomical causes may be subdivided into external and internal causes. The external causes may be either congenital or acquired while the internal are all congenital. The physiological causes of disturbance in the filling and emptying mechanism are the result of dyssynergia, known also as dyskinesia. There are two types of dyssynergia, the hypertonic and the hypotonic. The site of the basic disorder in the former is at the sphincter of Oddi, and in the latter, in the gall bladder wall.

Anatomical Causes (Mechanical)

The changes in structure found to initiate the process of gall bladder disease by interference with the outflow of bile are present, and exert their influence throughout the course of the disease. Their significance may be lost and is apt to be overlooked in the advanced stages of the disease unless one be intent upon seeking the initiating fac-

TABLE

DISORDERS RESULTING IN DISTURBANCES IN FILLING AND EMPTYING MECHANISM OF GALL BLADDER

A. ANATOMICAL CAUSES (MECHANICAL)

- 1. External-Congenital or Acquired
 - (a) Adhesions-Congenital or Inflammatory
 - (b) Abnormal Cystic Artery
 - (c) Pancreatic Inflammation Edema, Fibrosis with Common Duct Involvement
 - (d) Tumors of Pancreas and Extra-Hepatic Bile Ducts
- 2. Internal-All Congenital
 - (a) Convoluted Cystic Duct-Valve of Heister Obstruction
 - (b) Septa-"Phrygian Cap"

B. PHYSIOLOGICAL CAUSES (FUNCTIONAL)

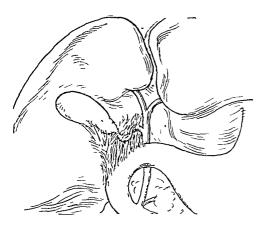
- ı. Hypertonic Dyssynergia
- 2. Hypotonic Dyssynergia

tors. A knowledge of their existence and detection is important in selecting a surgical procedure to deal with the entire scope of the disease as well as in making a correct prognosis regarding the ability of the chosen procedure to completely eradicate the disease process, or merely to remove the superadded complications of the irremovable basic disorder.

EXTERNAL

a. Adhesions

As every surgeon knows, adhesions are very frequent in the upper abdomen. They can seldom be shown to be the positive cause of gall



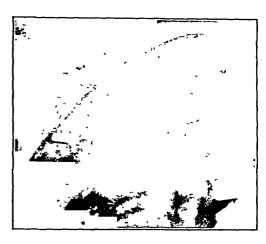


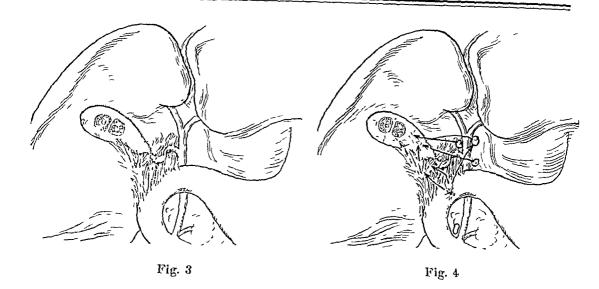
Fig. 1

Fig. 2

bladder disturbance but are considered to be the initiating factor for gall bladder disease in approximately 10 per cent of patients in this group. Their formation may be congenital as in an abnormal development and persistence of the cystic duodenal fold, or acquired from inflammation in adjacent structures such as duodenal ulcer or duodenitis. The acquired adhesions when present offer an additional direct route for the lymphatic spread of infection to the gall bladder.

The symptoms in a patient with adhesions are irregular attacks of colicky pain. The mechanism of these attacks of pain is explained as being due to the development of a pressure stimulus to the nerve endings in the gall bladder wall by the exertion of emptying bile through the partial obstruction offered by the distorted cystic duct (Fig. 1). In sensitive patients, an expression of a burning or tugging sensation in the right upper quadrant is a characteristic complaint. The characteristic roentgenograms show a small, densely concentrated gall bladder shadow with no visualization of the cystic duct (Fig. 2). The duodenal drainage is not distinctive.

Cholecystectomy results in the complete cure of the patient's symptoms. This is to be expected by reason of the fact that the scope of the disorder is entirely contained in the gall bladder. If, however, operation is not performed and the condition persists, there occurs a pathological stasis of bile. Precipitation of crystals, usually cholesterol, occurs and the formation of cholesterol stones results (Fig. 3). In this stage and for as long as the stones remain free in the gall bladder cavity, the



symptoms are the same as in the pre-stone stage. A roentgenogram shows normal concentration and negative shadows if no infection intervenes.

Should infection be superimposed on the gall bladder in this stage by spread, for example, from a concomitant duodenal ulcer (Fig. 4), then calcium bilirubinate is laid down on the cholesterol stone or stones and the mixed type of stone results, giving positive shadows in the roentgenogram. If the mucosa becomes inflamed, the concentrating function is affected and there is also faint or lack of concentration of dye as shown by roentgenogram. The short periods of discomfort are replaced by longer periods of a dull aching pain in the right upper quadrant. The course of the attacks begins mildly, increases in severity and gradually subsides, the whole extending over a period of four to ten days. Typical duodenal drainage shows no concentrated bile, crystalline sediment, and if infection is active, a positive culture. At this stage, while the infection is still limited to the gall bladder, cholecystectomy will cure the patient of symptoms and terminate the disease.

If, however, surgery is not done, sooner or later an engagement of the stone in the outlet of the gall bladder occurs with the development of a hydrops or empyema. When there are repeated attacks of empyema of the gall bladder, seepage of infected bile into the common duct occurs. Cholecystectomy at this point still cures the patient, and the uncomplicated contamination of the common duct will clear up. The outstanding findings in this stage are a palpable mass in the right upper quadrant and non-visualization of the gall bladder by roentgenography.

If, however, the gall bladder is not removed and the drainage of infectious material into the common duct persists, the infection becomes entrenched in the sacculi in the wall of the common duct. When the patient has reached this stage, simple cholecystectomy, although removing the obstructed gall bladder and with it the initiating cause of the disease, i.e., adhesions around the cystic duct, will not clear the common duct sacculi of the infection. The neglect of surgical treatment permits the residual nesting of organisms in the common duct sacculi to act as a focus of infection. Chronic and recurring acute attacks of choledochitis, i.e., "Charcot's fever" occur. A patient who has reached this stage requires medical treatment after cholecystectomy, viz., frequent duodenal drainages, bile salts, antispasmodics, etc. This is directed toward insuring a free flowing current of bile passing through the common duct to prevent stasis and wash out detritus. If this is not done, the patient is confronted with the danger of developing a common duct stone. Choledochotomy with removal of the stone is then required. Failure to remove the stone subjects the patient to biliary obstruction and possibly pancreatitis. Thus, the surgery in each stage becomes progressively more complicated. Fortunately in this category of gall bladder disease, patients tend to appear early for surgery and the terminal stages of persistent common duct infection and common duct stone are rarely encountered.

Summary: The prognosis for complete cure of the patient's symptoms and eradication of the disease process is reduced as time goes on. The basic initiating factor of adhesions around the cystic duct is removed by cholecystectomy at any time. The acquired factor of infection is eradicated by cholecystectomy up to the point when chronic involvement of the common duct sacculi occurs. At this stage more complicated operative procedures, e.g., cholodochotomy and "by-pass" operations between the common duct and duodenum, become necessary. Even these usually fail to permanently eradicate the infection once it has become firmly entrenched. Various medical procedures have proved disappointing in this regard as well. The subject will be discussed more fully in the section devoted to infectious cholecystitis.

The progressive nature of gall bladder disease; the complications superadded with the passage of time as described in this section will be seen to apply to the various other types of gall bladder disease to be discussed even though the basic initiating factors are different.

b. Abnormal Cystic Artery

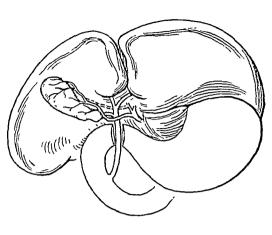


Fig. 5

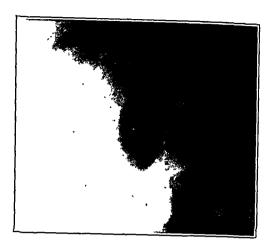


Fig. 6

PRE-STONE STAGE

MECHANISM

Cause (Fig. 5)

Any origin of cystic artery that necessitates its crossing the cystic duct to reach margin of gall bladder.

Effect

- 1. Compression of cystic duct.
- 2. Pain from pressure stimulus developed from increased effort of emptying against a partial compression of cystic duct.

TREATMENT

Cholecystectomy.

RESULT

Cure-initiating factor eradicated.

PROGNOSIS

Physiological effect of cholecystectomy is a moderate dilatation of common duct, normal process.

SPECIAL DIAGNOSTIC POINTS

History

- 1. Thought to be one of causes for cyclic vomiting, migraine, sensitive stomach, etc., occurring in early life.
- 2. Intermittent attacks of gall bladder colic. Prone to appear after loss of weight and liver ptosis. Amyl nitrite no relief of symptoms.

Roentgenogram (Fig. 6)

No enlargement of gall bladder. Distinct concentration of dye. Markedly delayed emptying after fatty meal.

Duodenal Drainage,

Small volumes of concentrated bile in response to stimulation. Crystalline sediment—cholesterol. Culture of duodenal specimen of bile negative.

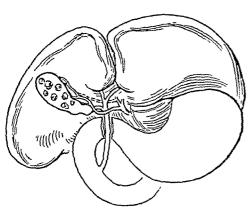






Fig. 8

STONE STAGE

MECHANISM

Effect-continued

- 1. Continuous process bile stasis. Uniform precipitation cholesterol crystals. Result large single or multiple stones (same family). (Fig. 7.)
- 2. Pain as in pre-stone stage.

TREATMENT

Cholecystectomy.

RESULT

Cure.

PROGNOSIS

Physiological dilatation of common duct. SPECIAL DIAGNOSTIC POINTS

History

Same as pre-stone stage.

Physical Signs

Negative.

Roentgenogram (Fig. 8)

Normal concentration. No enlargement. Delayed emptying. Negative stone shadow.

Duodenal Drainage

Normal response—small quantity. Crystalline sediment—cholesterol. Culture of bile—negative.

Summary: Cholecystectomy includes the entire disease producing factor and resulting changes up to this point of development.

Patients in whom the condition is not diagnosed, and those refusing operation during one of the two stages described above will in time develop the succeeding stages of gall bladder diseases. Usually, however, cholecystectomy is done early.

- c. Pancreatic Inflammation
- d. Tumors of Pancreas and Extra-Hepatic Bile Ducts

Causes "c" and "d" are included in Table I for completeness. While it is true that they interfere with the emptying mechanism of the gall bladder, such a disturbance is of minor importance compared with the primary condition.

a. Convoluted Cystic Duct-Valve of Heister Obstruction

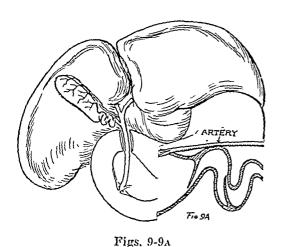




Fig. 10

PRE-STONE STAGE

MECHANISM

Cause

Ruffling of the cystic duct, the reason for which is not clearly understood. Can be easily demonstrated after removal and longitudinal section of specimen. The cystic artery will then be seen to pursue a straight course. The cystic duct is convoluted suggesting the accommodation of an elongated cystic duct to a shortened cystic artery. (Fig. 9.)

Effect

- 1. Pain resulting from a pressure stimulus developed by the gall bladder attempting to empty against a partial obstruction of the cystic duct due to a "foot valve" action of the valves of Heister. (Fig. 9A.)
- 2. Tendency in many instances to tubular enlargement of the gall bladder similar to that seen in hypertonic dyssynergia.

TREATMENT—Cholecystectomy.

PROGNOSIS-Cure.

SPECIAL DIAGNOSTIC POINTS

History

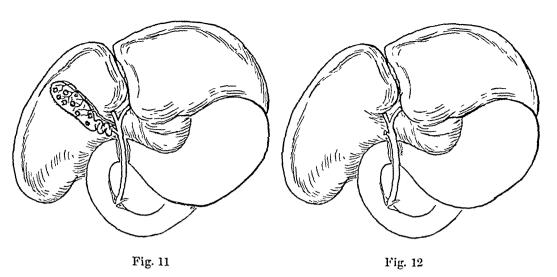
- Tendency to occur in individuals bordering on the ulcer type.
- 2. Irregular attacks of pain in R. U. Q. Severe colicky pain associated with eating heavy meals after periods of fasting.
 - Amyl nitrite no relief of symptoms.
- 3. Any condition in which there is prolonged storage of bile in the gall bladder predisposes to an attack, e.g., periods of starvation. Association with gastrointestinal upsets.

Roentgenogram

Dense concentration and frequently visible tortuous cystic duct. Delayed emptying (Fig. 10).

Duodenal Drainage

Irregular response. Crystalline sediment when dark bile is obtained. Culture of duodenal specimen of bile negative.



STONE STAGE

MECHANISM

Effect-continued

- 1. Bile stasis—all elements. Precipitation of crystals and stone formation. (Fig. 11.)
- 2. Pain as pre-stone stage.
- 3. Severe lancinating pain if stone becomes engaged in cystic duct.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. Physiological dilatation of common duct. (Fig. 12.)

SPECIAL DIAGNOSTIC POINTS

History

Irregular attacks of colicky pain, nausea and vomiting.

Amyl nitrite—no relief of symptoms.

Roentgenogram

Normal concentration of dye with negative stone shadows in nonobstructive cases. No visualization if gall bladder obstructed at time by stone in the cystic duct.

Duodenal Drainage

Irregular response to stimulation (difficulty in drainage). Crystalline sediment in dark bile.

Culture of duodenal specimen of bile negative.

Summary: Cholecystectomy will eradicate the causal mechanism and remove the effect of the condition. Neglect to remove the gall bladder will be followed by a continuation of the process. Superimposed infection or mechanical obstruction by stone leads to the final destruction of the gall bladder without the assistance of the basic factor. Infection can then spread to involve the common duct and result in common duct stone, obstruction and biliary cirrhosis. However, failure to relieve symptoms by medical means as a rule induces early operation.

b. Septa-Phrygian Cap

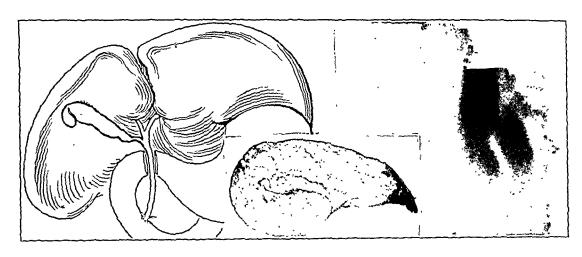


Fig. 13

Fig. 13A

Fig. 14

PRE-STONE STAGE

MECHANISM

Cause (Fig. 13, 13A)

Congenital septum interposed at some point in the cavity of the gall bladder, usually the fundus. Probably due to incomplete vacuolization of the cavity. (General incidence 6 per cent.)

Effect

- 1. Partial obstruction of the distal cavity.
- 2. Pain from pressure stimulus developed within the distal segment of the gall bladder attempting to empty against obstruction of the interposed septum.

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. Physiological dilatation of the common duct.

SPECIAL DIAGNOSTIC POINTS

History

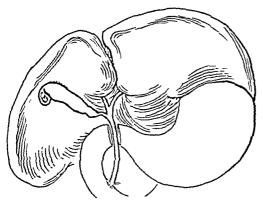
- 1. No specific symptoms directly attributable to deformity.
- Intermittent periods of pain and distress. Associated with eating heavy foods. Amyl nitrite – no relief of symptoms.

Roentgenogram (Fig. 14)

Normal visualization of body and fundus. Visualization of cap. Delayed emptying of cap. Frequently mistaken for extraneous adhesions.

Duodenal Drainage

Normal response. Crystalline sediment—cholesterol frequently present. Culture of duodenal specimen of bile negative.





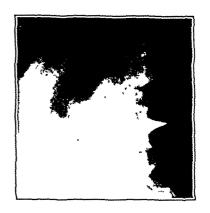


Fig. 16

STONE STAGE

MECHANISM

Effect—continued

- 1. Bile stasis—all elements. Precipitation of crystals and mixed stone formation in the cap. (Fig. 15.)
- 2. Complete obstruction. Stone engaged in aperture between cap and fundus.

TREATMENT Cholecystectomy.

PROGNOSIS Cure.

SPECIAL DIAGNOSTIC POINTS

History

Continuous distress of distention. Intermittent attacks of pain due to engagement of stone in the narrowed orifice of the distal segment.

Amyl nitrite-no relief of symptoms.

Roentgenogram (Fig. 16)

Normal concentration gall bladder. Delayed emptying and no visualization of cap. Possible negative stone shadow outside gall bladder shadow.

Duodenal Drainage

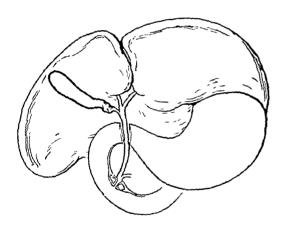
Normal response. Crystalline sediment - cholesterol - not distinctive. Culture of duodenal specimen of bile negative.

Summary: Whatever stage the disease process may have reached in patients in this group at the time of operation, that found in the cap appears to be most advanced. These findings suggest a progressive spread of the disease process from the cap to the gall bladder and then to the common duct. It resembles the course seen to occur in the gall bladder. Many patients are operated upon during an attack of acute abscess of the cap. Few progress to advanced common duct disease.

Physiological Causes (Functional)

There exists a difference of opinion as to the existence and importance of functional disorders as an initiating factor in the development of biliary tract disease. In the Gall Bladder Clinic at the Post-Graduate Hospital approximately two-thirds of all patients with gall bladder disease are believed to have had a disturbance in the filling and emptying mechanism of the gall bladder in the primary stage. A final analysis, especially that of follow-up findings shows the majority of patients to have had dyssynergia.

The functional disorder interfering with the filling and emptying mechanism of the gall bladder may be of two types. First, that due to an increased resistance to the flow of bile through the sphincter of Oddi—hypertonic dyssynergia, and second, that due to the diminished contractility of the gall bladder wall—hypotonic dyssynergia.



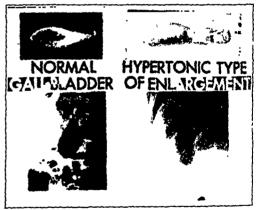


Fig. 17

Fig. 18

HYPERTONIC DYSSYNERGIA

The site of the primary dysfunction in hypertonic dyssynergia lies at the sphincter of Oddi at the lower end of the common duct (Fig. 17). There the increase in tone and hypertrophy is associated with one or other of two etiological factors. First, along with gastric hyperacidity and its associated duodenitis and papillitis. Second, as the result of a reflex spasm of the sphincter. The reflex may be from a distant primary site such as a diseased appendix or from the central nervous system. Whichever the factor concerned, the result is similar, namely, an increased resistance to the emptying of bile into the duodenum. The effect of this is a compensatory enlargement of the gall bladder which is

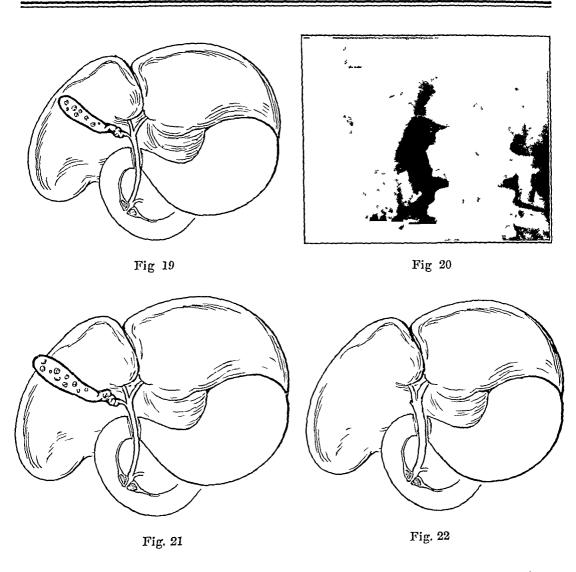
called upon to store larger quantities of bile. Hypertrophy of the gall bladder wall occurs as a result of the increased effort required to expel the bile. Pain is experienced from the development of a pressure stimulus to the nerve endings in the gall bladder wall due to these abnormal contractions, and a stasis of bile occurs due to the incomplete emptying of the gall bladder.

The patient experiences attacks of colicky pain in the right upper abdomen or epigastrium. Relief of the pain instantly after the inhalation of amyl nitrite is usually one of the characteristic features of this type of gall bladder disease. The roentgenogram shows normal concentration with delayed evacuation. The gall bladder is enlarged and tubular. The walls are thickened and hypertrophied (Fig. 18).

Cholecystectomy is contra-indicated in this type of non-calculous gall bladder disease for two reasons: first, the primary disturbance is not in the gall bladder. Secondly, if the gall bladder is removed, the pressure-regulating mechanism of the biliary tract goes with it. With continued dysfunction of the sphincter, therefore, the pressure within the common duct is greatly increased with a recurrence of symptoms. This type of patient requires medical treatment directed toward the cause of spasm of the sphincter of Oddi.

In the presence of duodenitis associated with hyperchlorhydria, a bland diet with antacids and antispasmodics are prescribed. If the spasm is believed to be reflex in nature, a diligent search is made for any focus of irritation especially in the abdomen. The psychic background of the patient is taken into consideration and often the assistance of the social worker is required for the proper approach to the cause of the condition. Unsuitable home conditions, unemployment and financial worries are all potent factors in the production of this type of dyssynergia.

Failure for such a patient to receive proper medical treatment leads to pathological bile stasis in the gall bladder. This is accompanied by sedimentation, crystallization and the formation of stones (Fig. 19). The symptoms and signs of increased pressure within the gall bladder continue as in the pre-stone stage. The characteristic roentgenogram shows stones in a normally concentrating and enlarged gall bladder (Fig. 20). Duodenal drainage shows irregular response to olive oil with crystalline sediment on microscopic examination. Culture of the bile specimen is sterile at this stage before the advent of infectious cholecystitis. It is customary to advise cholecystectomy in this stage of hypertonic dys-

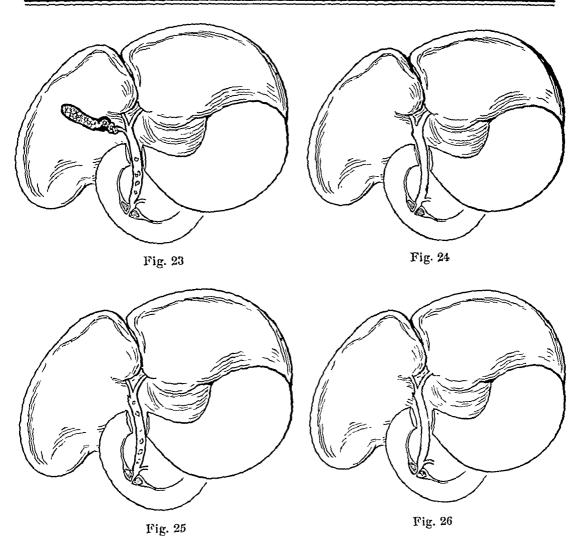


synergia with stones. This is done not with the intention of removing the cause of the disease process and of curing the patient's symptoms, but rather to prevent the impaction of a stone in the cystic duct. It must be emphasized that patients in this group are not cured by chole-cystectomy which eradicates only the result of the disease mechanism. The impaired bile duct mechanism remains beyond the scope of cholecystectomy.

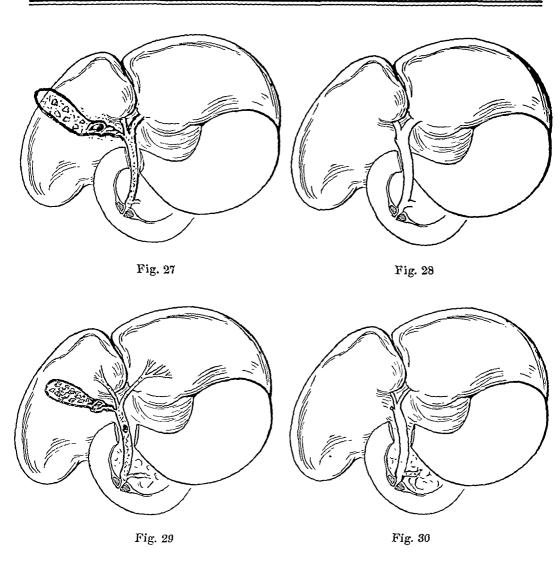
If the patient does not present himself for attention while in the free stone stage, one of the stones is likely to become impacted in the cystic duct. This results in a temporary hydrops of the gall bladder (Fig. 21). In the absence of infection, the gall bladder bile becomes absorbed. In this stage there are severe attacks of colicky pain in the right upper quadrant which respond irregularly to amyl nitrite but are

relieved somewhat by morphine. This is helpful in determining the stage of development of the disease in a patient in whom amyl nitrite has relieved previous attacks. Roentgenography shows concentration of dye before permanent engagement of the stone occurs in the cystic duct, and no visualization afterwards. Cholecystectomy, while removing the non-functioning gall bladder, still does not cure the patient's underlying pathology. After cholecystectomy (Fig. 22), the sphincter resistance to the flow of bile from the common duct into the duodenum is still increased. Under the circumstances, the intraductal pressure increases and the bile ducts dilate beyond the usual physiological extent following cholecystectomy. In an effort to accommodate the bile secreted by the liver which cannot freely enter the duodenum, the bile ducts concentrate the bile. The concentration, however, never equals that of the gall bladder. Such concentrated bile, when obtained after cholecystectomy, is evidence of sphincter spasm and stasis in the common duct. Continued spasm of the sphincter of Oddi leads to overdistention of the common duct and pain which is chiefly located in the epigastrium. To prevent symptoms after cholecystectomy, the cause of the sphincter spasm must be located and treated medically. Surgical treatment by cutting the sphincter from within has been attempted but not established as a procedure to be undertaken generally. In severe instances accompanied by recurrent jaundice, a "by-pass" choledochoduodenostomy may become necessary.

In a non-infected, obstructed, hypertonic gall bladder, absorption of water and bile elements by the mucous membrane does not cease. If the cystic duct obstruction remains for any length of time, the bile in the gall bladder at the time of the obstruction will be absorbed and the gall bladder will contract down around the stones. If the stones are small, and in this type of dyssynergia they usually are, one or more stones may be forced through the dilated cystic duct into the common duct (Fig. 23). In the absence of jaundice, such stones are often overlooked at operation. A contracted gall bladder containing small stones associated with a dilated cystic duct is an indication for exploration of the common duct (Fig. 24). Search for and recognition of this fact should prevent many secondary operations for removal of overlooked stones from the common duct. Patients with overlooked stones in the common duct (Fig. 25) constitute a difficult diagnostic problem. In the absence of jaundice, it is impossible with our present means of

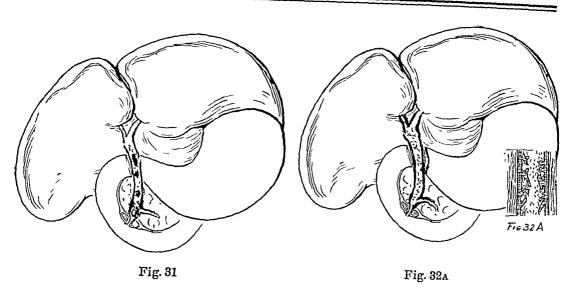


diagnosis to be sure that a patient's symptoms after cholecystectomy which appear resistant to medical treatment are not due to a common duct stone. On the other hand, choledochotomy is inadvisable as a routine procedure in all post-cholecystectomy cases with persistent pain. At one time the finding of a moderate number of crystals in duodenal drainage specimens was thought to be an indication of stones remaining in the common duct. Such an attitude resulted in several patients having an exploratory choledochotomy in whom no stones were found. All such cases should first be subjected to a strict, controlled, medical regime to rule out the possibility of the symptoms being due to uncomplicated sphincter spasm and its train of events. At the Gall Bladder Clinic the policy that has met with the greatest success is to keep the patient under observation and refrain from secondary common duct operations until jaundice appears. Removal of the common duct stones



(Fig. 26) must still be followed by medical treatment of the underlying sphincter spasm.

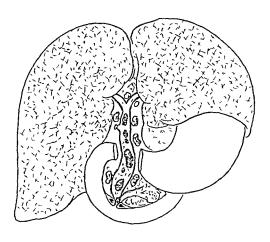
Infection is occasionally superimposed on one of the stages of hypertonic dyssynergia discussed above. If infection occurs in the stage of cystic duct obstruction, then empyema of the gall bladder results (Fig. 27). The route of the infection may either be by the blood stream, through the liver, or ascending through the duodenum. The characteristic attacks of colicky pain change to prolonged attacks of dull pain and tenderness in the right upper quadrant accompanied by fever and leukocytosis. The outstanding findings on physical examination are a palpable gall bladder like mass, tenderness and rigidity in the right upper quadrant. Roentgenography or duodenal drainage are not indicated



in the presence of a definite and characteristic gall bladder mass. Such a clinical picture is sufficient reason for an abdominal exploration. In those with signs of acute cholecystitis and no mass, roentgenography and duodenal drainage are indicated since the gall bladder is fibrotic and not liable to rupture during the investigation. Seepage of the infected bile occurs into the common duct which is contaminated by the offending organisms. A mild cholangitis may occur with slight fever and chills. However, removal of the gall bladder at this stage usually results in the clearing up of the superficial contamination of the common duct (Fig. 28).

In this stage, as in the non-infected, obstructed gall bladder, a stone may become extruded into the common duct. This is most apt to be found after the gall bladder, subjected to several attacks of a low-grade inflammatory nature, becomes thickened and contracted (Fig. 29). Recognition of the common duct stone at operation with its removal usually leads to the clearing up of the infection in the common duct (Fig. 30). The theory that an obstructed gall bladder or cystic duct might reflexly cause a common duct sphincter spasm was held for some time. Experience has shown this concept usually to be false as the spasm persists after removal of the gall bladder.

It should be stressed that medical treatment of the underlying tonic sphincter is important in these patients not only for the relief of their symptoms but to insure a free flow of bile through the common duct to clear out the organisms before they become firmly entrenched. If, however, common duct stones are overlooked (Fig. 31), then the cho-



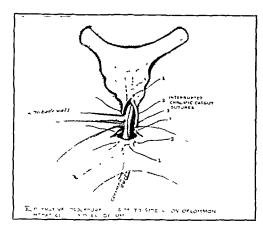


Fig. 32B

Fig. 32c

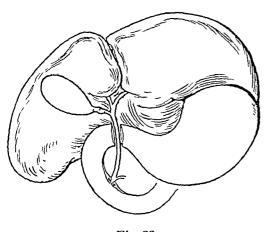
langitis will persist and in time the infection will become firmly entrenched in the sacculi of the wall of the common duct (Fig. 32 A). In addition, should the pancreatic duct unite with the common duct above the sphincter before entrance into the duodenum, the impaction of one of the common duct stones at the sphincter of Oddi exposes the patient to a reflux of infected bile into the pancreas with subsequent pancreatitis. Once the sacculi of the common duct have become a residual focus of infection, removal of the common duct stones will not usually be followed by eradication of the infection (Fig. 32). The patient at this stage has a chronic cholangitis. Periodic attacks of chills and fever with jaundice occur if the sphincter is not kept relaxed by medical treatment.

Ultimately the infection extends from the common duct up to the small bile canaliculi and then to the liver parenchyma itself—biliary cirrhosis. The involved liver is enlarged and hard; the common duct markedly dilated. Common duct stones are very apt to be reformed under these conditions in the common duct (Fig. 32B). To insure a free flow of bile and remove the pressure from the liver in this terminal stage of gall bladder disease, one may have to resort to a choledochoduodenostomy (Fig. 32c). Thus, what started out as a functional disorder of the biliary tract may over the span of years ultimately result in advanced organic disease. The entire course of gall bladder disease ending with biliary and splenic cirrhosis with portal obstruction has been observed in a 31 year old patient in our clinic. During the course of eight years of the disease there were performed a cholecystostomy with removal

of stones, cholecystectomy, and four operations for removal of common duct stones. The patient succumbed to gas bacillus bacteriemia following a fifth operation for removal of a reformed common duct stone. During the last operation a "by-pass" was made between the duodenum and common duct for the relief of the still existent dyssynergia and for permanent drainage of the incurable B. Welchi and B. coli infection of the common duct. Positive cultures of these organisms were found in the common duct at the last operation.

HYPOTONIC DYSSYNERGIA

The other type of dyskinesia which interferes with the filling and emptying mechanism of the gall bladder is the hypotonic type (Fig. 33). Here the site of the dysfunction lies not in the sphincter of Oddi, but in the gall bladder wall. It is what has been termed the "lazy gall bladder." Roentgenography shows a large, pear-shaped gall bladder which concentrates the dye with delayed evacuation after a fatty meal. The wall of the gall bladder in contrast to the hypertonic type, is thinned out and atrophic (Fig. 34).



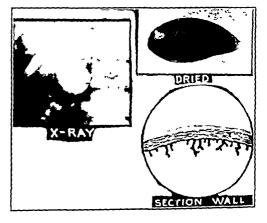


Fig. 33

Fig. 34

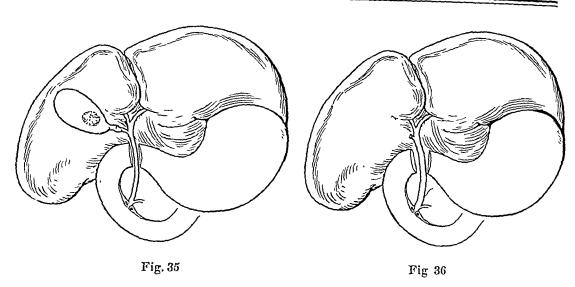
The patient often shows other evidence of hypotonia such as a low basal metabolic rate, low or absent free hydrochloric acid in the gastric juice, hypercholesterolemia, etc. These patients do not have colicky pain since the tone of the gall bladder wall and its contractions are not sufficient to increase the intravesical pressure to the point of developing an actual pain stimulus. These patients complain of mild discomfort in the upper quadrant associated with gastric irritability, belching and dis-

tention after meals. Because of the relative mildness of the symptoms, these individuals are infrequently seen in the Gall Bladder Clinic in this primary or pre-stone stage. Frequently they are treated in the Colon or Gastro-intestinal Clinic as in the early stages the stomach and colon show a similar tendency for dysfunction. The statement is frequently made that a physician's special interest in any of the fields into which these patients can be included is the controlling factor in the interpretation and treatment. A well executed routine of medical treatment has been credited with prevention of stones, improvement of gall bladder function and relief of symptoms in patients with hypotonic dyskinesia and bile stasis who have been followed continuously over a period of ten years.

The general incidence of this type of dyssynergia is much greater than is revealed in the analysis of the charts of patients coming to the Gall Bladder Clinic prior to stone formation. A better indication of the true incidence of hypotonic and hypertonic dyssynergia is found in a comparison of patients in the two groups in whom there has occurred stones in a gall bladder that is still functioning. Proper classifications upon the basis of all the findings in a large group of patients shows the relative occurrence to be about equal in the two types of dyssynergia. The laboratory work-up in such individuals shows normal liver function and usually hypercholesterolemia. Roentgenography shows concentration of the dye with delayed evacuation. Duodenal drainage usually shows hypochlorhydria and frequently a relative or absolute achlorhydria. No dark bile is obtained after the administration of magnesium sulfate, but is obtained after olive oil. Microscopic examination of the bile in characteristic instances shows large numbers of cholesterol crystals indicating a relatively increased concentration of cholesterol in the bile. Culture of the duodenal specimen of bile is negative when free hydrochloric acid is present in the gastric specimen.

When there is no free hydrochloric acid present, the duodenal culture will frequently show contamination by those organisms usually found in the nose and throat which have been swallowed and escaped the sterilizing action of the acid. In these instances a colon, typhoid or Welch bacillus is only taken to be supportive evidence of gall bladder infection.

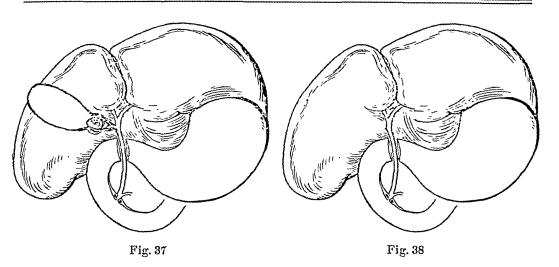
The condition responds well to medical treatment. Olive oil should be given between meals to enhance the stimulation of the gall bladder



and thus aid in its evacuation. All fats should not be eliminated from the diet since their effect upon the gall bladder wall is an essential part of the treatment. In patients with hypercholesterolemia, reduction of the cholesterol content of the diet is indicated. In those with hypochlorhydria or achlorhydria substitution therapy in the form of dilute hydrochloric acid with meals is a fixed routine. Correction of endocrine imbalances, such as hypothyroidism and obesity, is indicated as part of the general treatment.

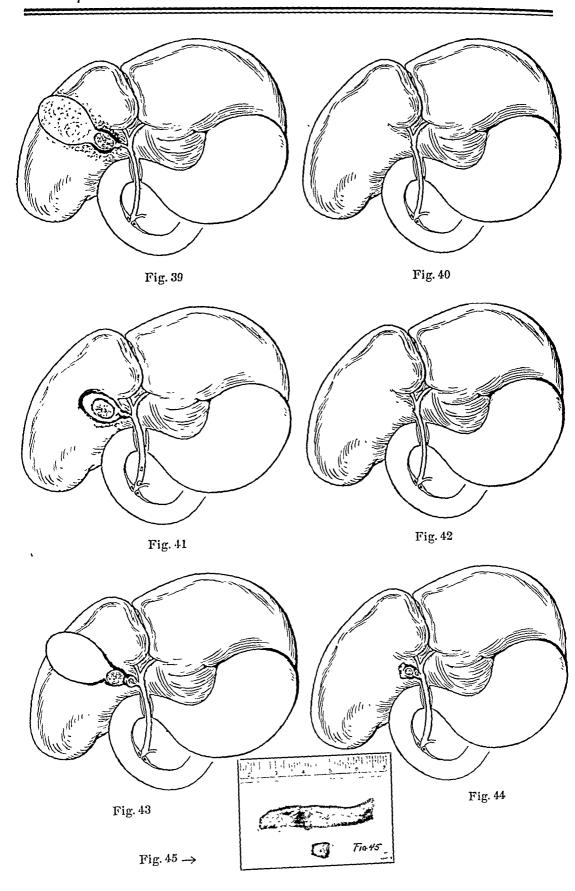
Bile stasis is eventually followed by the sedimentation of cholesterol crystals and ultimately stone formation if these patients are not treated successfully (Fig. 35). The symptoms in this stage are similar to the pre-stone stage so long as the stone remains free in the gall bladder cavity. Roentgenography reveals a stone in a functioning gall bladder. The duodenal drainage is similar to the pre-stone stage. Surgery is now indicated to prevent the mechanical complication of impaction of a stone in the ampulla of the gall bladder. Cholecystectomy cures the patient of all his symptoms since it removes the initiating cause of the gall bladder dysfunction, its wall, as well as the result, the stone (Fig. 36). The prognosis is excellent so far as recurrence of symptoms is concerned in marked contrast to the hypertonic type. The cure of the initiating process which eventually leads to advanced pathology is effected by cholecystectomy before stone formation as well as after. Operation is not necessary in the primary stage, however, since specific medical treatment will relieve the patient and seems to prevent stone formation.

The type of stone found in hypotonic dyssynergia is of the choles-



terol variety and is most often single. Since no additional symptoms are due to the presence of the free stone in the cavity of the gall bladder, it is often discovered during roentgenographic examination for other lesions. If not discovered, it has a tendency after an indeterminate period of time to become impacted in the ampulla of the gall bladder (Fig. 37). Once in this situation, it may give rise to symptoms resembling the colicky attacks of hypertonic gall bladder but to a lesser degree. Colic of this type is characterized by not being relieved by amyl nitrite inhalation. After the initial crisis during which the stone becomes impacted in the ampulla, no colic may be experienced by the patient since the gall bladder wall tends to atonia. Discomfort in the right upper quadrant may be experienced especially following fat meals which stimulate gall bladder contractions. Roentgenographic examination of the individual in this stage of gall bladder disease shows no visualization of the gall bladder. Duodenal drainage reveals no concentrated bile even after stimulation with olive oil. Cultures are negative as a rule. Cholecystectomy at this time promptly and completely cures the patient's symptoms and terminates the course of the development of gall bladder disease in that individual (Fig. 38).

Should infection be superimposed on an obstructed gall bladder, there is the development of an empyema of the gall bladder (Fig. 39). Cholecystectomy will still cure the patient if performed early enough (Fig. 40). If the obstructed gall bladder is subjected to repeated low-grade attacks of inflammation, its wall becomes thickened, fibrotic and contracted. Small stones in the gall bladder are apt to be extruded into the common duct after engagement of the larger stone in



the entrance to the ampulla (Fig. 41). It is important when the cystic duct is found dilated to make sure at operation that the common duct is free from stones. Removal of the gall bladder and common duct stones at this stage cures the patient and terminates the progress of the disease in that individual (Fig. 42).

In cases where the obstructing stone in the ampulla is the only stone present in the gall bladder, the cystic duct which is proximal to the stone and in open communication with the common duct becomes dilated. Stasis occurs with sedimentation and possible formation of small calculi in the cystic duct (Fig. 43). At operation, the relatively small, dilated cystic duct with its contained calculi is sometimes overlooked and is left after the gall bladder has been removed (Fig. 44). The danger of such an overlooked remnant is the possibility of the small contained stones entering the common duct. Four such instances have been observed and operated upon at the New York Post-Graduate Hospital in the past two years. Figure 45 shows the remnant of cystic duct removed from a patient. For twenty years following an operation for the removal of the gall bladder the patient was perfectly well. He then had an acute attack of epigastric pain associated with chills, fever, and jaundice. At operation an ampulla and dilated cystic duct remnant were found. A small stone composed of cholesterol with an outer covering of calcium bilirubinate (Fig. 45) was found impacted at the lower end of the common duct, which in this instance, united with the pancreatic duct before entering the duodenum. The probability is that the stone was either overlooked at the first operation or formed in the portion of cystic duct that was left. For some reason which cannot be determined the stone, after a prolonged period of residence in the cystic duct, entered the common duct where it became impacted at the lower end. The inner portion of the stone resembled gall bladder stone formation; the outer common duct stone formation.

The majority of patients having hypotonic dyssynergia are operated upon during the secondary period of the disease in which the stone is free in the gall bladder or shortly after the onset of the third stage with impaction and obstruction of the cystic duct. Neglected cases or those refusing surgery will, of course, continue on to the later stages with possible permanent common duct involvement. Since the mortality and morbidity rate increases with each successive stage of gall bladder disease it is advantageous to both the patient and the physician to utilize surgery early in the course of the disease.

TABLE II

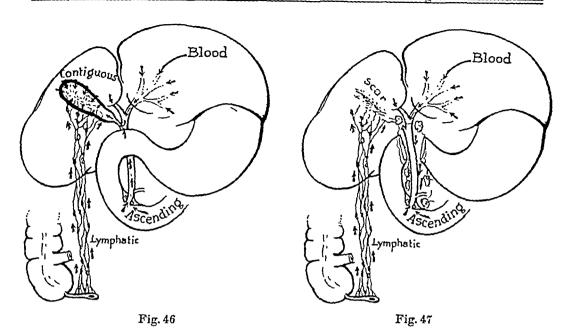
Disorders Resulting in Disturbances in the Concentrating Function of the Gall Bladder

- 1. Infectious cholecystitis
- 2. Reflux pancreatic juice
- 3. Abnormal concentration of special elements
 - (a) Bile Salts
 - (b) Calcium-Calcified Gall Bladder Wall
 - (c) Calcium Carbonate-"Milk of Calcium" Gall Bladder
 - (d) Cholesterol-Cholesterosis

DISORDERS AFFECTING THE CONCENTRATING FUNCTION OF THE GALL BLADDER

Fifteen to twenty per cent of the patients coming to the Gall Bladder Clinic in the primary stage of gall bladder disease, show disorders resulting in disturbances in the concentrating function of the gall bladder as listed in Table II. The most common cause in this group is infectious inflammation. In recent years, however, non-bacterial causes of inflammation have been suggested as capable of affecting the mucosa and of interfering with its concentrating mechanism. One of these is the reflux of pancreatic juice into the gall bladder. A prerequisite for this is the union of the common and pancreatic ducts above the sphincter of Oddi. The exact way in which the pancreatic juice affects the gall bladder is not entirely clear. However, that it is capable of producing a chemical inflammation under proper conditions is not doubted.

Disturbances in concentration may also be in the direction of abnormal concentration or secretion of special elements of the bile with or without the associated loss in bile concentration as a whole. Examples are: One, excessive concentration of bile salts. This has been shown experimentally to be capable of producing very marked inflammatory changes in the gall bladder. Two, calcium concentration. The result is a calcified gall bladder wall. This is rare. Only three cases have been seen in the clinic in the past twelve years. Three, calcium carbonate secretion. This is the so-called "milk of calcium" gall bladder. The contents are semi-solid and resemble light gray putty with the other



elements of bile reduced or absent. The etiology is believed by some authorities to be associated in some way with obstruction of the cystic duct, infection of the gall bladder wall and secretion by the wall of the calcium carbonate. Those cases which have been seen at the New York Post-Graduate Hospital of this type were found to be sterile when removed and cultured. Four, cholesterol concentration. The controversy as to whether the gall bladder execretes or absorbs the cholesterol found in its wall has not been determined. The fact is that there is an abnormal concentration of cholesterol in the gall bladder mucosa in cholesterosis, commonly called "strawberry gall bladder."

INFECTIOUS CHOLECYSTITIS

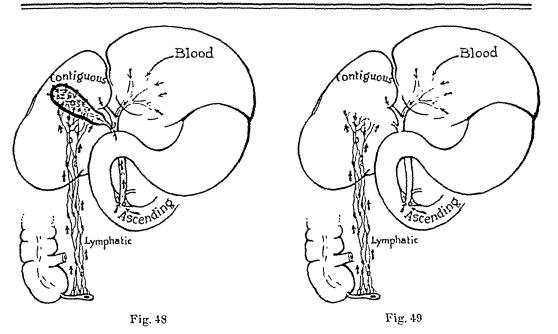
About 10 per cent of all patients coming to the Gall Bladder Clinic in the pre-stone stage have a demonstrable infection as the primary initiating factor of gall bladder disease. The presence of any one of the other initiating factors of gall bladder disease such as a tortuous cystic duct, dyssynergia, etc. together with infection, arbitrarily classifies the patient in the group of disturbances in the filling and emptying mechanism rather than as one of primary infectious cholecystitis. The infection may have reached the gall bladder via the blood; may have ascended from the duodenum; may have spread via the lymphatics from some other intraabdominal focus, e.g., duodenal ulcer (Fig. 46). While the history may

occasionally suggest the primary site of infection, it usually cannot be definitely determined at the time of examination. If the source is found, it is important to remove it. Removal of the gall bladder alone without the primary source will not always cure the patient of repeated attacks of infection and its effects on the biliary lymphatic zones (Fig. 47).

The special diagnostic signs of infectious cholecystitis are as follows:

- 1. Low-grade inflammatory pain of three to seven days duration.
- 2. Tenderness and rigidity in the right upper quadrant during an acute attack.
 - 3. Sub-clinical jaundice (Icteric Index 7-10 units).
- 4. Faint or absent visualization of the gall bladder on roent-genography.
- 5. Crystalline sediment of calcium bilirubinate on duodenal drainage.
- 6. Positive culture of the specific organisms in the duodenal bile.

The organisms most commonly found in chronic infectious chole-cystitis are B. typhosus, B. coli, B. Friedländer and rarely the streptococcus and staphylococcus groups. Cholecystectomy early in the course of the disease will result in the cure of the patient's symptoms and permanent interruption of the course of gall bladder disease when the site of the disturbance is contained within the gall bladder. Examination of the other intra-abdominal organs should be undertaken at operation, particularly the appendix as it is often the primary focus of infection. Structural deformities, sphincter of Oddi spasm, or gall bladder wall disturbances are not essential for infection to become residual in the gall bladder and cause a characteristic chronic infectious cholecystitis. The reason for infection becoming residual in the gall bladder is usually attributed to certain types of organisms being, or becoming, so resistant to concentrated bile that they are not affected by it. Such patients with chronic infection may not seek advice since the attacks of pain are of a low-grade nature and there may be long periods of freedom from symptoms. When a definite diagnosis of an existing chronic infectious cholecystitis is made, operation should not be unduly delayed as acute fulminating cholecystitis does occur in some patients prior to stone formation. The impression that this form of acute cholecystitis without stones is particularly dangerous probably springs from the serious type of organ-



isms that are capable of living and growing in a comparatively normal gall bladder.

In association with continued low-grade infection of the gall bladder, the composition of the bile is altered resulting in the precipitation of crystalline sediment, calcium bilirubinate, and the ultimate formation of small, irregular pigment stones "infectious stones" (Fig. 48). The clinical and laboratory findings in this stage are very similar to those found in the pre-stone stage. Surgery at this stage will still encompass and remove the condition as well as relieve symptoms and interrupt the course of development of the gall bladder disease process in the individual (Fig. 49). If, however, the patient does not seek advice, the next step is engagement and impaction of a stone in the cystic duct. Empyema of the gall bladder follows as there is infection already present (Fig. 50). At this stage there is severe pain with marked tenderness and rigidity in the right upper quadrant associated with fever, chills, and even sub-clinical jaundice. The patient appears fairly toxic and a palpable mass can be felt in the right upper quadrant. Roentgenography and duodenal drainage usually are not advisable at this time and are not deemed necessary as has been already pointed out. The clinical picture as outlined above is sufficient for an abdominal exploratory operation when a characteristic mass is present in the right upper quadrant.

The operation should be performed during the acute stage of infection, preferably between the second and fourth days. An analysis of the

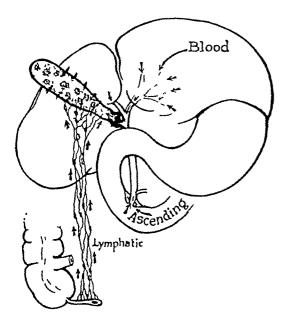


Fig. 50



Fig. 52

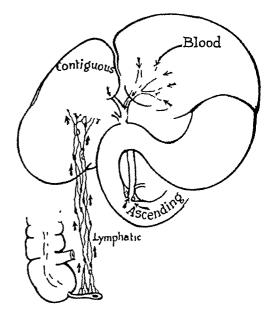


Fig. 51

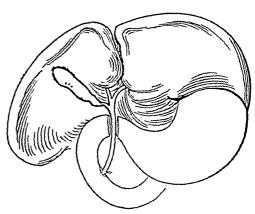


Fig. 53

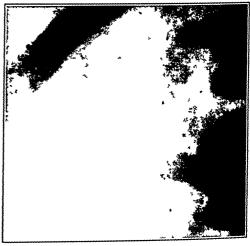
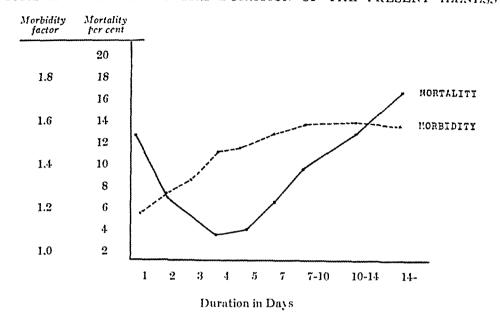


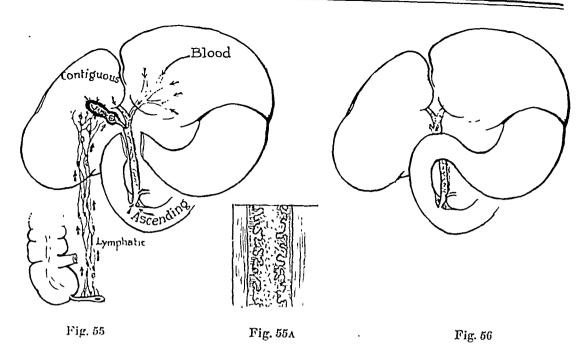
Fig. 54

TABLE III

THE MORBIDITY AND MORTALITY IN SURGERY ON ACUTE CHOLECYSTITIS IN RELATION TO THE DURATION OF THE PRESENT HANESS



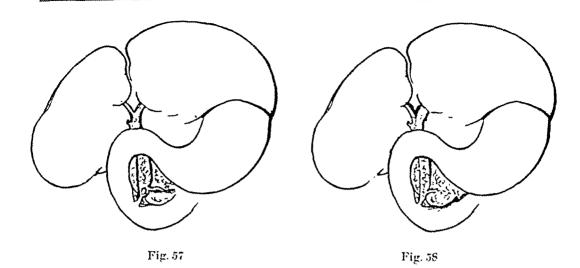
data on 500 patients with acute infectious cholecystitis at the New York Post-Graduate Hospital is shown in Table III. Mortality and morbidity are seen to increase after the fourth day of illness. The actual operative procedure to be followed will be determined largely by the condition of the patient. Under favorable circumstances, a cholecystectomy is done with the resultant cure of the patient (Fig. 51). Under unfavorable circumstances, however, one may be compelled merely to do a cholecystostomy (Fig. 52). It should be emphasized, however, that a cholecystostomy, in contrast to a cholecystectomy, is not a curative procedure. The infection remains in the gall bladder after removal of the cholecystostomy tube (Fig. 53). Such a gall bladder when followed by studies of its function by duodenal drainage, cultures and roengenogram examination over a period of many years never seems to regain its normal function nor rid itself of the B. typhosus or B. coli. Roentgenography following a cholecystostomy continues to show either faint visualization (Fig. 54) or no visualization of the gall bladder. Positive specimens of duodenal cultural examinations persist. Recurrence of the clinical picture with low-grade jaundice is the rule, and an indication that removal of the gall bladder as well as the stone is necessary for a cure in these cases. Recognition of this fact together with the good



results obtained by cholecystectomy probably led clinicians to the belief that the majority of disease processes in the gall bladder were on the basis of an initial infection.

Gall bladders which have been subjected to repeated episodes of empyema become contracted and fibrotic (Fig. 55). The infection extends into the common duct and after a period of time becomes firmly entrenched in the sacculi (Fig. 55A). After this has occurred, simple cholecystectomy will remove the primary site of the infection but does not cure the condition. It does not prevent the progress of the disease since the infection now has extended to, and permanently involved the common duct (Fig. 56). Medical and surgical attempts to eradicate chronic, residual infection in the common duct, especially that due to B. coli and B. Friedländer, have yielded poor results. Concentrations of sulfanilamide in the bile up to 15 mgm. per cent have failed to eradicate the B. coli and B. Friedländer. Similar disappointing results were obtained after the use of sulfathiazole, sulfapyridine, sulfaguanadine, phenolmercuric nitrite, vaccines and a host of so-called biliary antiseptics.

It is of the utmost importance, for two reasons, to insure a free flow of bile from a common duct in which chronic infection has become entrenched. First, stasis will result in stone formation and, secondly, acute pancreatitis in cases where the common duct and pancreatic duct unite must be expected following the impaction of the stone at the



ampulla with regurgitation of infected bile into the pancreas (Fig. 57). Removal of the common duct stone (Fig. 58) must also be followed by medical treatment or else the probability is that the patient will reform another stone. So long as a free flow of bile is assured, the latent infection may be expected to remain quiescent and cause little if any actual symptoms or disability.

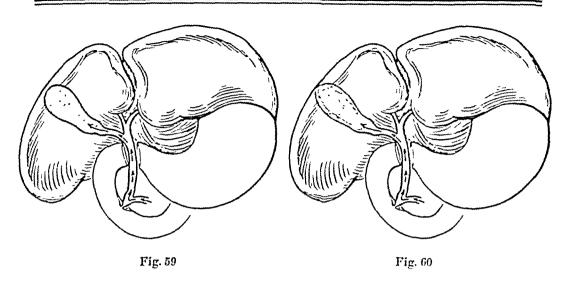
Summary: Formerly infectious inflammation was considered the sole cause of interference with the concentrating mechanism of the gall bladder. However, it is now realized that other factors beside infection may produce inflammatory changes. Infectious cholecystitis as an initiating factor constitutes about 10 per cent of primary gall bladder disease. The infection is at first localized in the gall bladder and may be permanently eradicated by cholecystectomy prior to extension to, and involvement of, the wall of the common duct. In the later stages the infection will permanently involve the common duct. At this time removal of the primary site, i.e., the gall bladder, does not influence the infection in the common duct. Attempts to eradicate the infection from a chronically involved common duct have until now been unsuccessful. Treatment is directed toward maintaining a free flow of bile to prevent stasis.

Failure of medical means, as indicated by repeated occurrence of attacks of pain, fever, chills and jaundice associated with signs of liver damage from recurrent stone formation with obstruction (Fig. 33) are all indications for surgical interference. 'By-pass' operations providing a permanent drainage outlet between the common duct and duodenum are useful in this and other types of chronic biliary obstruction (Fig. 32c).

REFLUX OF PANCREATIC JUICE

The possibility of a reflux of pancreatic ferments causing inflammatory changes in the gall bladder wall resembling those of bacterial inflammation has received much attention in recent years. It is significant that the pancreatic duct unites with the common duct above the sphincter of Oddi in the majority of people (various authorities quote from 45 to 84 per cent). Any obstruction, organic or functional, at the ampulla of Vater predisposes to the reflux of pancreatic ferments into the gall bladder. It probably occurs during periods of fasting even without the presence of obstruction. An analysis of the bile in 200 gall bladders removed at the New York Post-Graduate Hospital has confirmed the reflux of pancreatice juices in the majority of people. One or more of the pancreatic ferments were present in 59 per cent of the noncalculous gall bladders, in 74 per cent of gall bladders with stones and in the contents of 63 per cent of obstructed gall bladders. The presence or absence of pancreatic ferments in the gall bladder bile could not be shown by a study of the data to have any consistent effect upon the gall bladder wall or the formation of stones. The finding of pancreatic ferments in the gall bladder is of academic interest so far. Further study is necessary to determine just what importance such a reflux of ferments may have upon the development of pathology in that organ. On the other hand, there is little room for doubting the importance of this anatomical relationship in the development of acute pancreatitis.

The normal flow of bile in the fasting state is directed from the liver and bile ducts into the gall bladder where it is concentrated, a mechanism comparable to the flow of bile through the gall bladder in patients having a cholecystostomy. This process is conducive to a flow of pancreatic juice into the common duct and upward, following the general current, into the gall bladder. Obstruction of the gall bladder by stone, or its surgical removal, diverts the bile current between meals from the gall bladder to a continuous flow into the duodenum. Pathological pressure developed in the common duct by increased resistance to the flow of bile through the sphincter of Oddi permits the reflux of bile into the pancreas and the production of pancreatitis. The inflammatory reaction is greatly enhanced by the presence of bacteria. After the third stage of gall bladder disease has been reached, i.e., obstructed cystic duct and gall bladder obliteration, infection is usually present whatever the initiating cause of the disease. The anatomic relationship described, therefore, is of importance in the subsequent course of events.



PRE-STONE STAGE

MECHANISM

Cause

Reflux of pancreatic ferments into gall bladder. (Fig. 59.)

Effect

Questionable. Possible chemical cholecystitis. (Fig. 60.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

No pre-operative means of determining anatomical relationship of pancreatic and common ducts.

History

No characteristic symptoms of the existence of pancreatic ferments in the gall bladder at any stage of gall bladder disease.

Physical Signs

Not distinctive.

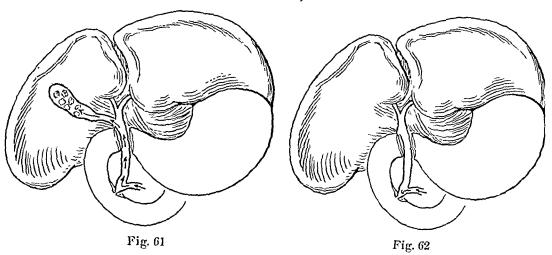
Roentgenogram

Not distinctive.

Duodenal Drainage

Not distinctive. Culture of duodenal specimen of bile sterile in all patients examined.

REFLUX OF PANCREATIC JUICE (continued)



STONESTAGE

MECHANISM

Effect

Questionable. Altered relations of constituents of bile. Precipitation of crystals. Formation of stones rich in calcium bilirubinate. (Fig. 61.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure. (Fig. 62.)

SPECIAL DIAGNOSTIC POINTS

History

Not distinctive.

Physical Signs

Not distinctive.

Roentgenogram

Not distinctive.

Duodenal Drainage

Not distinctive. Culture of duodenal specimen of bile sterile in all patients examined.

Summary: While the effect of pancreatic ferments on the gall bladder wall may be open to question, the union of the common and pancreatic ducts above the sphincter of Oddi is of great importance since reflux of infected bile into the pancreas may produce acute pancreatitis (Fig. 63). Pre-operatively the anatomical relationship of the two ducts cannot be determined. Postoperatively, however, in cases with tubes in the gall bladder or common duct, introduction of a contrast substance (hippuran, diotrast, lipiodol) often shows the union of the ducts (Fig. 64).

Reflux of bile into the pancreas is the result of pathological pressure in the common duct; the result of obstruction at its lower end. Com-

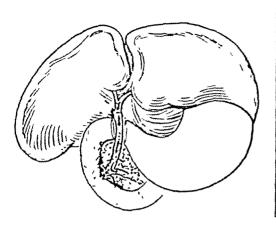




Fig. 63

Fig. 61



Fig. 65

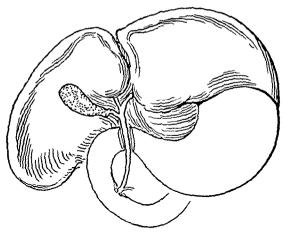
Fig. 66

Fig. 67

mon causes of this obstruction are impacted stone, spasm, or edema of the sphincter. Of the three, common duct stone is the most common. Figure 65 shows a stone in the lower end of the common duct in a patient in whom the anatomical arrangement of the ducts predisposed to pancreatitis. A cholangiogram done postoperatively (Fig. 66) reveals the stone removed. Such a patient requires careful postoperative medical management to prevent sphincter spasm and further reflux of bile into the pancreas. This is especially important if the bile is infected. In contrast, Figure 67 shows common duct stones in a patient in whom the common and pancreatic ducts do not unite above the sphincter of Oddi. Reflux of bile into the pancreas is not a danger in such a patient.

ABNORMAL CONCENTRATION SPECIAL ELEMENTS

a. Bile Salts





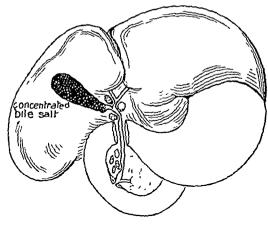


Fig. 69

MECHANISM

Cause

Excessive concentration of bile salts. Exact mode of action not definitely known. (Fig. 68.)

Effect

Inflammation of gall bladder. Gangrene of gall bladder wall. Very little inflammatory reaction preceding gangrene. (Fig. 69.)

TREATMENT
Cholecystectomy.

PROGNOSIS
Uncertain.

SPECIAL DIAGNOSTIC POINTS

Etiology not determinable preoperatively.

History

Same as any other acute inflammatory cholecystitis.

Physical Signs

Jaundice without anemia. Rigidity in right upper quadrant. Excessive rise in temperature.

Roentgenogram

Faint or no visualization of the gall bladder. Roentgenography rarely done in presence of marked acute symptoms.

Duodenal Drainage Not diagnostic.

Summary: The finding of acute inflammation in gall bladders containing dark sterile bile during the first two days of an acute attack have suggested a chemical basis for the inflammation. Marked excessive concentration of bile salts results in early, dry gangrene. The entire gall bladder wall may be found to have the lifeless appearance of tissue sud-

denly deprived of its blood supply. Operation in such instances after the fourth day of illness reveals abscess formation at the site of the gall bladder with positive cultures. This finding has led to the suggestion that the primary cause is chemical followed by the superimposition of infection. Less marked concentration under similar circumstances will occasionally reveal an acutely inflamed gall bladder with enlarged lymph nodes at the cystic duct and along the common duct.

b. Calcium-Calcified Gall Bladder Wall



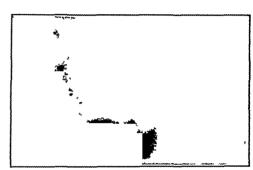


Fig. 70





Fig 71

MECHANISM

Cause

Not definitely known.

Effect

- 1. Deposition of calcium in wall of gall bladder. (Fig. 70.)
- 2. Formation of calcium carbonate stones. (Fig. 72.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Cure.

SPECIAL DIAGNOSTIC POINTS

History-No definite symptoms unless stone becomes impacted.

Physical Signs

Frequently associated with lowgrade jaundice.

Roentgenogram (Fig. 71)

Irregular calcification of gall bladder wall.

Duodenal Drainage

Irregular response—not diagnostic. Culture of duodenal specimen of bile sterile in all patients examined.

c. Calcium Carbonate-"Milk of Calcium" Gall Bladder

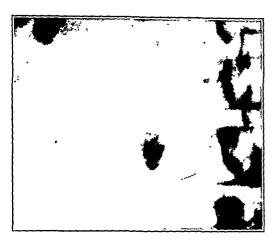


Fig. 73

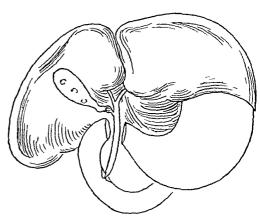


Fig. 74

MECHANISM

Cause

Not definitely known. Believed associated with inflammation and obstruction of cystic duct.

Effect

- (a) Abnormal appearance of calcium in gall bladder cavity.
- (b) Calcium carbonate deposited "milk of calcium." Resembles putty.
- (c) Calcium carbonate stones formed.

TREATMENT Cholecystectomy.

PROGNOSIS Cure.

SPECIAL DIAGNOSTIC POINTS

History

Right upper quadrant or epigastric distress with excessive gas.

Physical Signs

Associated with low-grade jaundice in patients seen in this clinic.

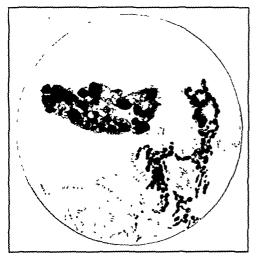
Roentgenogram

- (a) Outline of gall bladder after dye given frequently mistaken for normal visualization.
- (b) Lack of alteration in gall bladder shadow after fatty meal often mistaken for retention of dye in gall bladder.
- (c) Roentgenography without dye gall bladder visible. (Fig. 73.)
- (d) Stone may be seen in cystic duct although gall bladder well visualized. (Fig. 74.)

Duodenal Drainage

Not diagnostic. Culture of duodenal specimen of bile sterile in all patients examined.

d. Cholesterol-"Cholesterosis"





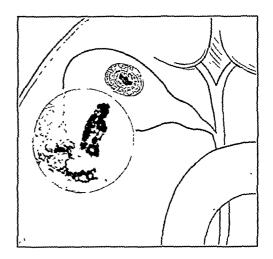


Fig. 76

MECHANISM

Cause

Unknown.

Effect

(a) Deposition of cholesterol in mucous membrane of gall bladder (Fig. 75.)

(b) Possible detachment of papilloma which forms center for stone formation. (Fig. 76.)

TREATMENT

Cholecystectomy.

PROGNOSIS
Cure.

SPECIAL DIAGNOSTIC POINTS

History

Not distinctive—see summary.

Physical Signs

Negative.

Roentgenogram

Normal visualization. Rapid emptying of gall bladder after fatty meal suggestive but not conclusive.

Duodenal Drainage

Not significant. Culture of duodenal specimen of bile sterile in all patients examined.

Summary: An examination of the data in patients found at operation to have cholesterosis does not reveal symptoms suggesting the presence of this condition. It is frequently found associated with all stages of gall bladder disease; even in the common duct wall in advanced choledochitis. As a rule, its presence is not suspected and looked for pre-operatively. At present it does not play an important part in the concept of gall bladder disease. It may possibly be found to be of greater importance as our knowledge of cause and effect increases.

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TABLE IV

DISORDERS IN BLOOD AND METABOLISM RESULTING IN DISTURBANCES OF THE GALL BLADDER

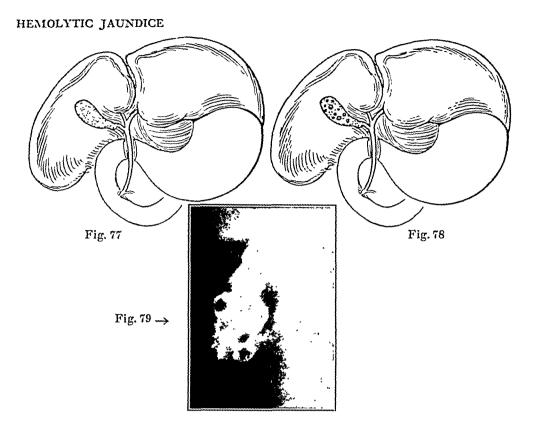
- 1. Hemolytic Jaundice Congenital hemolytic icterus, "sickle cell" anemia, etc.
- 2. Cholesterol Metabolism
 - (a) Pregnancy
 - (b) Obesity

DISORDERS IN BLOOD AND METABOLISM AFFECTING THE GALL BLADDER

The last etiological group to be considered includes those general disorders which manifest themselves in disturbance of gall bladder function (Table IV). Included is hemolytic jaundice, a blood dyscrasia in which there is an increased fragility of red blood cells, e.g., congenital hemolytic icterus, "sickle cell" anemia, etc. The excessive breakdown of red cells leads to an increased concentration of calcium bilirubinate in the bile with subsequent precipitation and stone formation. Pigment stones have been found in the gall bladder and biliary tract in 60 per cent of cases with congenital hemolytic icterus.

In pregnancy and obesity the basic disorder is an upset in the cholesterol metabolism.

Strictly speaking the initial upset in this group is in the concentration of special elements in the bile. In contrast to the abnormal concentration of special bile elements listed in Table II, however, the initiating mechanism lies *outside* the biliary tract. The condition is not limited solely to the biliary tract, but merely expresses itself there in one form. Thus, the calcium bilirubinate stones in hemolytic jaundice, and the cholesterol stones in pregnancy and obesity are usually found in an otherwise normally functioning gall bladder. Once stones have formed, however, the superadded progressive complications already described (impaction of stone in cystic duct, etc.) may occur.



MECHANISM

Cause

Hemolysis of red blood cells.

Effect

- 1. Excessive amount of calcium bilirubinate in bile. (Fig. 77.)
- 2. Precipitation of pigment and stone formation. (Fig. 78.)

TREATMENT

Cholecystectomy.

PROGNOSIS

Uncertain. May form common duct stones.

SPECIAL DIAGNOSTIC POINTS

History

No symptoms referrable to gall bladder. Hemolytic jaundice, anemia, etc.

Physical Signs

Jaundice, anemia, increased red blood cell fragility with spherocytosis, "sickling," etc. Positive indirect Van den Bergh reaction.

Roentgenogram

Normally functioning gall bladder. If stones present, well visualized. (Fig. 79.)

Duodenal Drainage

Normal response. Crystalline sediment—calcium bilirubinate. Culture of duodenal specimen of bile sterile in all patients examined.





Fig. 80

Fig. 81

CHOLESTEROL METABOLISM

a. Pregnancy

The association of pregnancy and gall stones is well known. Experimentally, the gall bladder in pregnant pigs has been shown to be less responsive to the stimulating action of cholecystokinin than in the non-pregnant. Furthermore, the blood and bile in pregnant women has a higher concentration of cholesterol than normal. These two factors, stasis and a relative preponderance of cholesterol in the bile, predispose to the precipitation of crystals and the formation of stones. This mechanism may occur in any type of gall bladder. Figure 80 shows the gall bladder of a patient seen at the clinic complaining of distress in the right upper quadrant. Figure 81 shows the gall bladder of the same patient seen after a pregnancy had occurred. Many negative shadows, all of the same size, can be seen. The probability is that the intervening pregnancy with its stasis and upset in cholesterol metabolism was responsible for the stone formation.

b. Obesity

Here again the basic disorder as regards the gall bladder is an upset in the cholesterol metabolism. The exact association between obesity and gall bladder disorder is not known. Most obese individuals, however, with associated gall bladder disturbance tend toward hypotonic dyssynergia.

THE DIAGNOSIS AND PROGNOSIS OF BRAIN TUMORS*

GILBERT HORRAX[†]

must be kept in mind constantly. First, has the patient a brain tumor or some other type of intracranial lesion which simulates tumor, and second, if a tumor is present neurologic knowledge and diagnostic methods, the first of these questions can be answered in practically every case provided the patient or his responsible relatives consent to thorough diagnostic measures. With regard to the second question, we are likewise usually able to locate the tumor exactly, but its pathology, predictable in a large and ever increasing percentage of cases, often cannot be determined prior to operation.

DIAGNOSIS

From the standpoint of diagnosis, there are roughly two clinical types of brain tumor: first, that which presents the well-known symptoms and signs of brain tumor, and secondly, that which presents many different neurologic or other findings but lacks the usual textbook picture.

With regard to the first type, when the complaints include headaches and vomiting and the ophthalmoscope shows choking of the optic disks, the burden of proof is obviously on the person who says that the diagnosis is not brain tumor. Nevertheless, there are certain other conditions which may produce this time-honored triad, and from which tumor must be differentiated. Among these are brain abscess, which may be suspected from a preceding infectious process, particularly an old otitis media, chronic mastoiditis, frontal sinusitis. scalp infection or bronchiectasis, to mention a few of the common possibilities. Another con-

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dition which is recognized as a clinical entity is the so-called "increased intracranial pressure without tumor," that is pseudotumor or arachnoiditis, which may be surmised when pressure symptoms, together with choked disks are acute, and the neurologic signs absolutely lacking. Often this little understood, possibly inflammatory disturbance seems to be almost epidemic in character. The diagnosis can be made with certainty only by a ventriculogram which shows normal-sized ventricles in normal position. Malignant hypertension may also cause headaches and choked disks. As a rule, the diagnosis can be made on the basis of the blood pressure findings, together with evidence of cardiorenal disease, but when the systolic and diastolic pressures are only moderately elevated, an air study may be indicated to be perfectly sure that a growth is not overlooked. A chronic subdural hematoma may simulate tumor almost exactly, but the bilateral trephine holes used in carrying out the ordinary ventriculogram and situated over each parieto-occipital region, will almost inevitably disclose a unilateral or bilateral hematoma and thus confirm the diagnosis before the air study is done. Meningovascular lues and tuberculous meningitis should also be mentioned as conditions sometimes mistaken for brain tumor, but as a rule there is little difficulty in differentiating them by means of spinal fluid studies.

I feel obliged to extend a word of caution in using lumbar puncture as a diagnostic measure in probable brain tumor. It is seldom necessary in making such a diagnosis and, except in rare instances, adds nothing which cannot be learned more safely by means of careful neurologic study together with a ventriculogram when indicated. In trained hands and with due caution, accidents are rare, but the danger is not purely theoretical, avoidable deaths having occurred in practically all large neurologic and neurosurgical clinics where this measure is undertaken routinely.

Under the second category of patients, that is, those who do not have choked disks and other usual manifestations of brain tumor, a variety of neurologic, ophthalmologic and otologic evidences may have led to the suspicion of tumor, and for this reason, the patients must be studied with such a lesion in mind. Among these symptoms I would mention particularly focal or generalized convulsions, slow visual failure with some degree of unexplained optic atrophy, changes of personality in the absence of cerebral arteriosclerosis or evidence of some clear-cut recognizable psychosis, increasing unilateral deafness, staggering, or a

slowly progressive hemiparesis which at first was thought to be due to cerebral thrombosis.

In patients with these symptoms and signs, the diagnosis may be difficult and entail elaborate study. A careful, chronologic history together with a neurologic examination are the first requisites, but in addition, roentgenologic examinations of the skull, visual field examinations with small test objects, caloric tests, electro-encephalogram, and either an air encephalogram or ventriculogram may all be necessary. At times a careful lumbar puncture may give useful information.

As a rule, the differential possibilities are such conditions as cerebrovascular disease, multiple sclerosis, labyrinthitis, posttraumatic headache and dizziness, platybasia, and occasionally, primary anemia or psychoses of various sorts.

SITUATION AND PATHOLOGY

With regard to the situation and pathology of brain tumor, it is well known that the brain harbors a large variety of tumors, but what is not so well known is the fact that the life histories and the clinical syndromes characteristic of certain types of growths in certain situations have been worked out in elaborate detail in the course of the last twenty-five years. The late Harvey Cushing and his associates were responsible for much of this information.

For the purposes of our present study, we may divide brain tumors into two groups so far as the diagnosis of their situation and pathology is concerned. In the first group are those tumors which as a rule can be recognized with a high degree of accuracy from the symptoms and objective neurologic or other clinical signs, which they produce and in the second, those which give no characteristic evidence of their whereabouts.

In a general way, but by no means without exception, the first group includes largely those tumors which are benign, encapsulated and favorable for complete enucleation, that is, certain of the meningiomas, the acoustic neuromas, the pituitary adenomas and some benign but uncommon tumors such as cholesteatomas or slowly growing gliomas which give characteristic roentgenologic findings. Also in this category are the somewhat less favorable tumors such as the congenital cysts of Rathke's pouch, pinealomas and some aneurysms which should be classed as tumors. In this short discussion only the briefest possible men-

tion can be made of the diagnostic features of these tumors.

- 1. Meningiomas are the well-known, firm, encapsulated growths which are attached to the dura and occur in various favorite situations. Those under the frontal lobes give slow mental changes, loss of the olfactory sense, and often optic nerve atrophy on one side and papilledema on the other, the syndrome of Foster Kennedy. The small meningiomas situated just above the sella turcica cause gradual failure of vision, optic nerve atrophy and bitemporal defects of the visual fields. They are differentiated from pituitary adenomas because the sella is not enlarged and pituitary functions are not lost. Meningiomas arising from the greater wing of the sphenoid often cause great hypertrophy of the bone in this area by tumor cells infiltrating the bone, and the eye on the affected side is pushed forward to a considerable degree (unilateral exophthalmos). Other meningiomas at various places over the cerebral convexities frequently cause characteristic bony enostoses and an increase in vascularity of the skull which is shown by the roentgenogram.
- 2. The syndrome of acoustic tumors, which are the common cerebellopontile angle growths, is now well known. A careful, chronologic history usually starts with unilateral tinnitus followed by increasing deafness in that ear, and then numbness on the same side of the face, staggering, headache, and finally, failing vision, dysarthria and dysphasia if the tumor is not recognized and removed. Objectively there is slow nystagmus, ataxia and an absent caloric response from the affected ear. The optic disks may show choking.
- 3. Adenomas of the pituitary gland present little diagnostic difficulty. The familiar triad of optic atrophy, bitemporal hemianopsia and a greatly enlarged sella turcica, as shown in the roentgenogram, can hardly be mistaken, especially when there are the usual evidences of pituitary dysfunction, such as amenorrhea in the female, loss of libido and feminine distribution of body hair in the male, a lowered basal metabolic rate, and increased carbohydrate tolerance. Occasionally an aneurysm in this situation may give signs which are extremely similar.
- 4. Of the more unusual tumors whose site and character often may be recognized by the roentgenogram, diploetic cholesteatomas show a scalloped outline of bony excavation. Craniopharyngiomas or Rathke's pouch cysts cause deformation of the sella often with calcification above it, and either choked disks or optic atrophy according to whether they protrude posteriorly or anteriorly to the chiasm. Certain calcified gli-

omas, notably the oligodendrogliomas, are likely to have a characteristic roentgenogram, and the same is true of some intracranial aneurysms. Pinealomas are rather rare tumors, but may be recognized with fair accuracy from the neurologic features of pupillary inactivity to light and loss of conjugate movements of the eyeballs upward above the horizontal plane. They also give a characteristic ventriculographic picture which shows the tumor shadow in the posterior portion of the third ventricle.

The tumors in the second group seldom or never give any neuro-logic or other evidence of their situation, hence this must be determined by means of air ventriculography. This group includes many of the large, infiltrating gliomas of all kinds occupying the so-called silent areas of the brain. Indeed the diagnosis of a considerable number of cerebellar tumors, both benign and malignant, can be made with certainty only by resorting to air studies, since cerebellar symptomatology may be inconclusive. In addition to the gliomas both above and below the tentorium, meningiomas which do not show roentgenologic changes or a characteristic clinical syndrome will likewise require air studies. Other tumors in this second group are those in the region of the third ventricle, a good many of the metastatic growths, and certain of the more rare lesions which need no enumeration.

PROGNOSIS

Needless to say, the outlook for permanent useful life in a patient harboring a brain tumor is dependent upon complete removal of the tumor without damage to important neighboring structures. Recurrence is inevitable unless the growth is entirely removed. Although some tumors grow very slowly and partial removal may give several years of freedom from symptoms, nevertheless our aim should be total extirpation of all benign growths except in extremely rare circumstances. Fortunately with modern equipment including electrosurgery and a well organized neurosurgical team, this is now possible in a high percentage of cases. Even in the infiltrating tumors, if a radical, subtotal extirpation is done, and I believe it should be, many patients will have surprisingly long periods of normal and useful life, occasionally five or even ten years if a slowly growing glioma is encountered.

The use of roentgen therapy for malignant brain tumors, with the exception of medulloblastomas, pinealomas and occasionally oligoden-

drogliomas has been completely disappointing, in my experience, and any favorable results after such roentgen therapy could just as well have been due either to the tumor removal or to the decompression which may have been left at the time of operation. Roentgen therapy deserves a trial in cases of early pituitary adenoma since a certain number of these tumors are radiosensitive, but it is tragic to see, not infrequently, patients who have become blind because this treatment was persisted in until the optic nerves became completely atrophied when an earlier operation might have restored nearly normal vision.

Concerning prognosis we can now be infinitely more specific than in the earlier years of neurosurgery when all brain tumors were regarded as relatively hopeless lesions, and the occasional long survival of a patient from whom a tumor had been removed was regarded as an interesting and rare surgical curiosity. The largest and most exhaustively studied series of verified brain tumors is that of Cushing, and in 1935 Eisenhardt reported the end results of these patients, listing those who had survived five years or longer. There were 2,000 cases in the series, and of these about 1,500 survived the operation and the subsequent period of hospitalization. Of this number, almost one third or 33 1/3 per cent had lived from five to twenty-eight years up to seven years ago. Obviously, many more would now be included in this survival list if the figures were brought up to date.

These statistics did not include a discussion of useful life, but at least they are most enlightening from the standpoint of actual survival, especially since this series dates from the very beginning of neurosurgery in this country. If only the last ten or fifteen years had been reviewed, the results would unquestionably have been even more striking. Also, the series considers all tumors, benign and malignant, but obviously the patients who survived longest are those who harbored growths favorable for complete removal.

In an attempt to obtain information about useful survival of patients with brain tumor, that is, those who after operation either went back to their original occupation or to some useful type of work, I reviewed my own series of 400 verified tumors from November, 1932, to June, 1939. This therefore gives a follow-up period of from three and a half to eight years. It was apparent, as would be expected, that those who had done best were in the group of benign or favorable tumors, that is, those from whom the tumor could or should have been completely removed,

and it was on this group only that I made my study.³ Well over one-half of all my patients fell into this favorable category, and although the tumors of many others were radically but subtotally extirpated and the patients had useful survival periods, they were not included in this group.

The favorable tumors consisted mostly of meningiomas, acoustic neuromas, pituitary adenomas, gliomatous and hemangiomatous cysts of the cerebellum, and a rather large group of uncommon tumors, the names of which are not pertinent here. All told, this favorable group comprised 218* of the 400 tumors, or 54.5 per cent. The operative mortality was 12.3 per cent (27 patients), and 16 other patients had died at various times subsequently. Of the survivors, 27 have severe disabilities which prevent them from engaging in useful occupations, leaving 148 patients or 67.8 per cent of the original 218 who are living and actively engaged in some form of work. If one takes the percentage only of the 191 who survived the operation, the figure of useful life rises to 77.6 per cent.

In general terms, therefore, somewhat over half of all brain tumors are favorable for complete extirpation, and of those patients who survive operation about three-fourths ought to be returned to useful life. As stated before, this figure does not include a fair number of patients who have tumors which cannot be completely eradicated and yet who may have several years of useful existence after their tumors have been radically but subtotally removed.

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Gramicidin is without bacteriostatic effect by intravenous, intramuscular, or subcutaneous injection. The reason for the absence of effect when it enters the circulation is not known. It has been suggested that it may be due to the fact that it is so highly insoluble, or there may be substances in the body, yet unknown, which inhibit its effect.

Experiments in animals and man indicate that it is highly effective against infections by local application. An intraperitoneal injection of 0.002 mg. of gramicidin protects the mouse against 10,000 fatal doses of the pneumococcus. This is, of course, essentially a local action, since no protection is conferred by the intravenous injection of the drug. In this type of experiment, it is from 25 to 50 times as potent as tyrocidine.

Both tyrocidine and gramicidin are toxic in animals. The fatal dose for gramicidin in mice is approximately 12 mg. per kg., and for tyrocidine approximately 80 mg. per kg. The bacteriostatic action, however, involves amounts which are very far below the range of toxic doses.

Gramicidin has been put to use in studies of human infections, in patients with ulcers of the skin, skin infections, mastoids, empyema, osteomyelitis, and other conditions. It is applied locally. The application of 10 mg. of gramicidin, for example, to a staphylococcus ulcer of the leg, results in complete sterilization of the area and signs of healing in twenty-four hours. A dose of 20 to 70 mg. placed into the mastoid cavity has yielded striking clearance of the infection. It has been placed within the empyema cavity of hemolytic streptococcus infections, with some rather dramatic results, but it may be readily realized how difficult it is completely to sterilize such areas, in view of the fact that the compound produces its effect by local action, and the area that is to be disinfected must be readily accessible.

It is obvious that the therapeutic applications of gramicidin are limited. It is not particularly valuable in mixed infections. It is only useful against Gram-positive organisms, and there is some indication that the presence of Gram-negative organisms exerts an inhibiting effect on gramicidin. It is of relatively little value where the circulation is poor, and where sinus formation is present. It may be noted, however, that most war wounds are caused by Gram-positive organisms6 and, in conditions in which the wound can be fully exposed to the antibacterial agent, the limited experience that now exists indicates, that gramicidin is a chemotherapeutic agent of some promise.

In 1929 Fleming described an antibacterial substance liberated by

a culture of a mould closely related to the Penicillium notatum, which he called penicillin. This material has been extensively studied more recently by a British group at Oxford,⁸ and others.⁹

The chemical constitution of this material is not yet known. It is not a pure substance. It is fairly stable. It is freely soluble in water. The potency of the material elaborated by the mould varies with the conditions under which it is cultivated. They have now produced a product which is a thousand times as strong as the original material used by Fleming. For purposes of comparison in study, it is assayed for its bactericidal power by comparison with an arbitrarily chosen standard penicillin. In therapeutic tests they used a penicillin which possesses about 40 to 50 units per mg. of the powder, and dosage is usually expressed in these units.

Penicillin is destroyed in acid solutions, and therefore is not suitable for oral administration. It has, however, been introduced directly into the duodenum in man, with evidence of considerable absorption over a period of several hours. It is highly effective by intravenous injection. It is less effective by intramuscular injection, and least effective by subcutaneous administration. Its toxicity is very low. An intravenous injection of 400 mg. per kg. (about 16,000 units) causes no toxic effects in mice. An intravenous dose of 15 mg. per kg., equivalent to about 50,000 units for a man, causes no effect on the blood pressure or respiration of cats, although perfusion of the cat's heart with 1:5,000 solution gives rise to some depression which is reversible. A single intravenous injection of 200 mg. (about 10,000 units) in man is also without toxic effects.

It is fairly rapidly excreted, apparently chiefly by the kidneys. About half of an intravenous injection appears in the urine in a few hours, and only traces are present in 6 to 8 hours. A large part of the amount found in the urine may be recovered in a purified form as the active material. It appears that some of it is inactivated in the body, although the mechanism is not known. Tissue slices do not seem to destroy it.

Its antibacterial action is very high, and many pathogenic organisms cease growing *in vitro* with a dilution of one part in one million. Under similar conditions, its antibacterial action has been found to be as much as 300 times as potent as sulfapyridine or sulfathiazole. In tissue culture medium it appears to have the same order of activity as gramicidin against Gram-positive cocci. ¹⁰ It inhibits the growth of the staphylococcus, streptococcus, gonococcus, meningococcus and others. It does not

appear to be effective against the Bacillus coli, proteus, or influenzae.

Like gramicidin and the sulfonamides, it does not act in the manner of an antiseptic agent, since it does not interfere with oxygen uptake of organisms even in a concentration of 1:1,000. In some specific way it interferes with the growth of bacteria, but does not destroy them. For example, even after the incubation of the staphylococcus in a 1:1,000 solution of penicillin, it will resume its growth readily in subculture, which signifies that the drug is bacteriostatic, although there are conditions under which it may kill the organism. In this respect it resembles the sulfonamide drugs.

In animal experiments it has been found highly effective against staphylococcal and streptococcal infections, and also against infections with anaerobic organisms of gas gangrene.

It is noteworthy that penicillin does not affect leukocytes except in very high concentrations, greater than 1:500. In this regard it is more favorable than most of the locally acting antiseptics, since the leukocytes are known to play an important role in the control of infection.

Penicillin has been used in several experimental studies in man. In staphylococcus bacteriemia, in osteomyelitis, in empyema, in pneumococcic meningitis, and in other infections, some striking results have been obtained. Thus far it seems to have failed in bacterial endocarditis. In bacteriemias and septicemias the blood may be cleared of organisms within two to three days after very large doses such as 100,000 units a day. The most effective mode of administration at the present time is by intravenous injection of several thousand units every few hours. It has also been applied locally to superficial infections, infections of the eye, in a 1:5,000 solution.

Penicillin is still in the experimental stage. It is difficult to produce it on a large scale. Its biological properties and the preliminary results suggest interesting possibilities for this compound, both as a local and as a systemic chemotherapeutic agent.

Sulphamethazine: Among the new sulfonamides, I wish first to speak briefly about sulphamethazine. It was prepared in Great Britain, and the first report of its clinical use was made in May, 1942 by Macartney and his collaborators, 12 of Manchester. It is a dimethyl sulfadiazine. The two methyl groups take the place of two hydrogens on the pyrimidine radical. It is a pale yellow crystalline material. Its bacteriostatic effects lie in the same range as those of sulfadiazine. Its speed of absorption and

of elimination are essentially similar to those of sulfadiazine. The absorption is apparently not complete because the total recovery in the urine is only about 50 per cent of the dose or less, also similar to sulfadiazine.¹³ It has the advantage of high solubility. Whereas sulfadiazine is soluble to the extent of 18 to 51 mg. per 100 cc. of water at 37° C., in the pH range of from 5.5 to 7.5, the new compound under similar conditions has a solubility of from 191 to 297 mg., thus about 10 times as soluble in the acid range and about 6 times as soluble in the alkaline range. The acetylated sulphamethazine is nearly 5 times as soluble as the acetylated sulfadiazine in the acid range but, strangely, somewhat less soluble than the acetylated sulfadiazine in the alkaline range, namely, 176 mg. against 248 mg. per 100 cc. When given in amounts of 4 grams as the initial dose and 2 grams every 6 hours, an average blood level of 6 mg. is reached. Conjugation in the blood stream does not seem to be very active and at the higher blood levels amounts only to about 10 or 15 per cent of the total. The sodium salt of this compound is very soluble and 1 gram may be injected intravenously in 3 cc. of solution without reactions. The concentration of the drug in the cerebrospinal fluid is fairly high, some 50 to 80 per cent of that in the blood. Macartney and his co-workers used the drug successfully in pneumonia, meningitis and gonorrhea. The toxic effects were few, mild nausea and vomiting, which sometimes disappeared while the drug was continued. The most important point seems to be that there were no crystals in the urine, even though the concentration of the drug in the urine rose to very high levels. In view of the fact that a significant increase of non-protein nitrogen in the blood occurs in approximately 1 per cent of the cases with sulfadiazine,14 the new compound is of particular importance. There has been relatively little experience with sulphamethazine, but the indications are promising that there may here be a compound with the high efficiency of sulfadiazine and, because of its high solubility, relatively free of the action which is a source of some of the most troublesome toxic effects, namely, those due to renal irritation and obstruction.

Sterilization of Intestine: During the past two years interest has developed in the possibility of sterilizing the bowel by the local action of the sulfonamides. For this purpose it was necessary to secure a potent soluble sulfonamide, the action of which would be largely confined to the gastrointestinal tract. Up to the present time complete sterilization of the bowel has not been achieved, but interesting advances in that

direction have taken place.

Sulfaguanidine was the first agent belonging to this group which was actively studied. Its synthesis and physical properties were described in 1940 by Roblin and his collaborators.¹⁵ Its pharmacology, antibacterial actions, toxicology, and therapeutic uses have since been studied by several workers.¹⁶

Sulfaguanidine is soluble in water at body temperature to the extent of approximately 0.2 per cent. Its absorption from the intestinal tract is fairly slow, and its excretion is rapid. It appears to be conjugated to a considerable extent, somewhat more than sulfapyridine, but the conjugated form of sulfaguanidine is more soluble both in water and in urine than that of sulfapyridine. This favors a lesser tendency to precipitation in the kidney. From in vitro and in vivo studies of its antibacterial activity, it stands among the more potent sulfonamide compounds.

The property of high solubility and poor absorption, as well as rapid excretion, suggested its use in the treatment of intestinal infections such as dysentery, cholera, typhoid, and in the sterilization of the intestinal tract for operations on the bowel. Some success has been attained in the treatment of bacillary dysentery.17,18 The stools were cleared of the Flexner bacillus by this drug in a group of dysentery carriers.19 After a daily dose of 4 grams for a week, a total of 28 grams, to a series of patients in one epidemic, the Flexner bacillus disappeared from the stools fairly promptly, by comparison with the results in a similar epidemic which served as a control.20 It has been used with some apparent success21 in surgery of the large bowel prior to operation; primary healing in cases that usually run a more stormy course; recovery in some cases in which infection would ordinarily prove fatal; marked reduction in the concentration of coliform bacteria in the feces. Large doses were used, of the order of about 3 grams every 8 hours for several days. The experience with this drug has turned out to be, however, quite variable.22 Sulfaguanidine has proved to be far from a safe drug. Although in most cases the sulfonamide level in the blood rises only to about 2 to 4 mg., there are others in which it may rise as high as 7 mg. per cent. A number of toxic symptoms similar to those for other sulfonamides have also been observed, namely, nausea and vomiting, headaches, drug fever, conjunctivitis, hemolytic anemia, oliguria and hematuria.

In connection with the use of sulfaguanidine for reducing the population of coliform bacteria in the intestine, the observations of Macken-

zie et al.²³ are of great interest. They, as well as others, found that sulfaguanidine inhibits the growth of laboratory animals (mice and rats). They further found that even in those periods when the rate of growth was normal, the thyroid gland showed hyperplasia, hyperemia, and hypertrophy. It grew, in some animals, to from 3 to 8 times as large. Animals (rats) also developed bleeding from the eyes. These effects were prevented by simultaneous feeding of p-amino benzoic acid and yeast. They pointed out that this phenomenon results from the fact that the organisms of the bowel play a part in the synthesis of essential nutrients, and that sulfaguanidine, by destroying these organisms, gives rise to a nutritional deficiency. To what extent this factor may operate in humans is unknown, but a potential source of trouble is suggested.

Sulfaguanidine does not appear to be quite as favorable a drug for intestinal sterilization as the latest member of this group, namely, succinyl sulfathiazole (sulfasuxidine). The synthesis of this compound was described by Moore and Miller²⁴ in 1942. Succinyl sulfathiazole is not very soluble in water, about 70 mg. per 100 cc. at body temperature, but when dissolved with sodium bicarbonate it forms a sodium salt which is very soluble, and 50 per cent aqueous solutions can be readily made. It is one of the most innocuous of all the common sulfonamides.²⁵ A daily oral dose of 1 gram per kg., amounting to about 2 ounces for an average man, given for five weeks to a dog produces no appreciable toxic effects, although the coliform count of the feces may fall off from an average of 10 million per gram to less than 100. It is not possible to kill mice with its oral administration. By intraperitoneal injection in mice, the compound suspended in oil or the sodium salt dissolved in water is less than one-tenth as toxic as sulfaguanidine. The drug is very poorly absorbed, since only about 5 per cent is recovered in the urine and large oral doses produce blood levels of only about 3 mg. in the dog and the monkey (1 to 5 grams per kg. per day), less than half of which is in the form of sulfathiazole and the rest in the form of succinyl sulfathiazole. Large doses also appear to be without influence on the growth of rats or the morphology of the thyroid, although in the light of the experience with sulfaguanidine, this requires further study. Essentially similar data have been obtained for the monkey.

This compound forms soluble salts so readily that it is much less likely than other sulfonamides to form crystal deposits in the urine, although there is some evidence that crystal formation may occur.

Striking effects have been reported following the use of succinyl sulfathiazole in intestinal surgery.26 Doses of 0.5 gram per kg. (about 35 grams) during the first day, and about half as much daily divided into 6 fractions at 4-hour intervals, give rise to concentrations of free sulfathiazole in the feces ranging from 85 to 200 mg. per 100 cc. These exercise a strong local bacteriostatic effect. At the end of about a week, in most cases, the therapeutic effects are in evidence, namely, a marked lowering of the coliform count and of other bacteria, as well as changes in the character of the stool. The stool becomes semi-fluid; it assumes a gelatinous appearance and becomes relatively odorless. The reports indicate that the use of this drug makes it possible to eliminate purgation during the pre-operative period, which tends to result in dehydration. Some of the troublesome and dangerous complications of surgery on the bowel seem to be effectively controlled, namely, gaseous distention, abdominal pains, abscess and postoperative peritonitis. It is much too early to evaluate fully the therapeutic uses and disadvantages of succinyl sulfathiazole. However, the properties of this compound, as well as the limited experience, suggest that it may prove to be an adjuvant of some importance in intestinal surgery and in the treatment of intestinal infecrions.

In the time that remains, I shall bring together a few of the developments of the past year or two relating to the group of sulfonamides as a whole, especially to trace a few of the threads that seem to run through the whole story. For a long time to come, progress in sulfonamide therapy is likely to be gauged not only in terms of new agents, but in terms of better understanding of the behavior and the uses of the older members. What seems to have become an endless succession of drives for different and better compounds followed immediately the discovery of sulfanilamide. The accounts of these activities, quite naturally, lay stress on dissimilarities-how much more effective one member is than another in the treatment of pneumonia or meningitis or some other infection; how much more quickly one is absorbed than another, or more quickly or more slowly eliminated; how much more toxic one is than another, and so forth. That information is, to be sure, of great importance, but it is also one of the most irregular aspects of the path of progress. No sooner, for example, does one report state that sulfacetimide is the most valuable agent in the treatment of urinary infection,27 when another records experience indicating the probability that the advantages do not exist.²⁸ The welter of discordant experience and difference is a source of confusion. I think it helps us find an anchor in therapy if we set our minds on the similarities among these compounds and on some of the differences in their properties and behavior which one may, perhaps, in a practical sense, ignore.

Mode of Action: The mode of antibacterial action of the various sulfonamides appears to be essentially the same. The view that has the most satisfactory support, is that the sulfonamide exerts its bacteriostatic effect by interfering with the function of p-amino benzoic acid in the bacterial cell, or some compounds in the cell with an essentially similar chemical structure. There is some suggestion that it may interfere with the metabolism of the bacterial cell at other points also, as indicated by the antagonism with methionine, and proteose-peptone.29,30 The concept involving p-amino benzoic acid was suggested by D. D. Woods in 1940.31 This compound is a member of the B-complex and is apparently an essential part of the enzyme system of certain bacteria. The molecule of sulfonamide appears to be able to occupy the place assigned to p-amino benzoic acid in the cell, but without being able to perform the function assigned to that position. Under these conditions bacteria cease to grow. There are other hypotheses which have already been largely discarded. A similar fate may be in store for this one before the story is fully known.

Dosage: The effective dosages and the plans of administration of the sulfonamides in common use for their systemic effects are, from the experience which has accumulated, essentially identical-sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and sulphamethazine. The goal should be a maximum concentration in the blood for a few days rather than a prolonged course of smaller doses.³² A dosage level which does not produce a marked effect in a few days is not likely to prove more successful over a long period of time unless there is impaired excretion which automatically, by cumulation, raises the effective concentration in the blood. For severe infections, the first daily dose is 10 grams for the average adult; 4 grams in the initial dose, and 1 gram every 4 hours day and night. This is followed by 6 grams daily given in a similar manner. This is continued until the temperature is normal, for two to three days. If the temperature does not fall rapidly to normal but settles down to lower levels, the dose may be reduced to 5 grams or 4 grams daily. The decision concerning this change requires judgment of the

various factors in the particular case. The guide to variations from the average plan of dosage is the condition of the patient, the presence or absence of therapeutic or toxic effects. If two days elapse without a therapeutic effect, the blood level should be determined. If it is below 3 or 4 mg., the dose should be increased, or several doses given intravenously.33 In less severe infections, the doses are smaller. The infections of the urinary tract appear to respond on the whole to smaller doses, 3 to 4 grams daily.27,28

There are isolated experiences which indicate that some infections due to resistant types and strains of organisms may require much larger doses, with resulting blood concentrations of sulfonamide away outside the levels which may be attained with any fair degree of safety, levels of the order of 40 or 50 mg. or more, for effective control. I have reference particularly to cases of subacute bacterial endocarditis.34 It is not often possible to attain such levels without a dangerous degree of renal blockage with the available compounds. In such cases, of course, the danger of the disease and of the drug must be carefully weighed against each other.

With daily doses of 6 grams, patients acquire blood levels of about 10 mg., and with daily doses of 3 grams, levels of about 5 mg. Two patients receiving the same dose of the same drug may show widely different blood levels due to differences in speed and completeness of absorption, and speed of elimination. While there is a general relationship between the therapeutic effectiveness and the blood concentration of the drug, there are so many factors in human infections which influence that relationship, that in one individual with, for example, a pneumococcus pneumonia, a 4 mg. concentration of the drug will produce a satisfactory therapeutic result for which another patient may require a blood concentration twice as high.33 Not all the factors responsible for this fact are known, but there has accumulated a great deal of experimental data which suggest reasonable explanations. The bacteriostatic power of the sulfonamides depends upon such factors as the quality of the medium in which the organism grows, the temperature, the pH of the medium, the concentration of organisms, the resistance of the strain, and the speed with which the liver acetylates the drug, since the more it is conjugated, the less is its bacteriostatic action. Some or all of these factors may differ from patient to patient.

How often the sulfonamide blood level should be determined in the

course of treatment is a question that cannot be answered in a manner that will apply to every case. If, during the use of the full doses which we have just discussed, the blood concentration is determined after approximately 20 grams, or at the end of the second or the middle of the third day, a great many cases of poisoning will be prevented, since by that time the concentration will reveal whether the patient is one whose tendency it is to accumulate the drug beyond the level of the average individual. This, again, is a rule which will not cover all cases, but helps in a large proportion of them.

There are several pharmacological differences between the members of the sulfonamide group which should theoretically alter the plan of dosage, but the accumulated experience indicates that these factors do not essentially alter the therapeutic results for the different compounds, if the doses and the intervals between them are applied as I have outlined. Nevertheless, these differences need to be kept in mind for the case of special problems that arise. Sulfanilamide and sulfathiazole are rapidly absorbed. A given dose is likely to cause a peak concentration within an hour or less. In the case of sulfapyridine and sulfadiazine, absorption goes on over a period of four to six hours. In the case of the first two, elimination is quite rapid, and within six to eight hours the blood level has fallen off considerably; within twenty-four hours they are almost completely eliminated. In the case of the latter two, elimination proceeds slowly and two to three days elapse before the larger part of the dose is excreted. Cumulation to toxic levels is therefore more likely with these, a fact that needs to be taken into consideration in those cases in which the drug is used over a more protracted period of time.

Toxic Effects: The sulfonamides are potentially dangerous drugs. There are thus far no exceptions. The list of toxic effects is now quite formidable. No bodily system is immune. It is entirely possible that the toxic effects of the sulfonamides are part and parcel of the effects of these drugs on cells, whether they are bacterial or human cells. It is, therefore, conceivable that the mechanism of action which results in the disturbed metabolism of the bacterial cell results in the phenomenon of toxicity in the human cell.³⁵

The toxic effects are fairly well known and perhaps do not require detailed discussion, except to refer briefly to the question of what to do when they occur. This matter, of course, cannot be disposed of by the simple statement that if toxic symptoms occur, discontinue the drug,

since such a decision may also be fraught with hazard.

The renal complications are the ones which present the most pressing problems. They are due chiefly to the precipitation of the insoluble, compounds, mainly the acetylated form of the drug in the tubules and renal pelvis. The crystals irritate the kidney, giving rise to renal bleeding, and obstruct the production and flow of urine. These crystals are rarely found in the case of sulfanilamide, which is very soluble, but occur in two-thirds of the cases receiving sulfapyridine or sulfathiazole, and in one-twelfth of the cases receiving sulfadiazine. 14,36 The drug should be discontinued if there is a gross hematuria, also if red blood cells appear in the urine. At this point we should recall the need for a careful search for red blood cells before the drug is started, at least as careful as after the drug is given. Red blood cells are often present in the urine of patients requiring sulfonamides. A very helpful sign is obtained from the urine output. A urine output of at least a liter a day should be maintained. If the urine output in relation to the intake begins to fall off and cannot be maintained, injury of the kidneys is taking place which may lead to anuria, several cases of which have been reported. Fluid intake does not need to be restricted in sulfonamide therapy. The idea of restricting fluids in order to secure higher concentrations of the drug has been abandoned even in the treatment of infections of the genito-urinary tract,37 since it is now the belief that the drug acts mainly before it enters the lumen of the tubular tract.88

Alkalinizing the urine tends to diminish the liability to crystal formation. It has been observed³⁸ that sodium bicarbonate given in doses equal to those of sulfadiazine and sulfathiazole cuts in half the frequency with which crystals are found in the urine. A point which probably has a bearing on the matter is the observation that in water at 37° C., the conjugated sulfadiazine which has a solubility of 25.5 mg. per 100 cc., at a pH of 5.5, becomes 10 times as soluble, namely, 248 mg. per 100 cc., at a pH of 7.5. Under the same conditions, the conjugated sulfathiazole increases its solubility by five times.³⁰ However, the solubility characteristics of chemical agents cannot always be predicted. It is not the same in water as in urine, and not the same in dilute urine as in urine containing larger amounts of other materials.⁴⁰

In the case of blood changes, a fall of the red or white cell count, or hemoglobin is a fairly common toxic effect. There is no choice but to discontinue in the more severe types of poisoning such as hemolytic

anemia or agranulocytosis. The milder changes often present a dilemma. The drug should be discontinued if the white cells fall below 4,000.³⁷ In this connection it is very disappointing to discover this number of white blood cells after the drug has been given and no control blood count to which it might be related. Every patient receiving sulfonamide should have a blood count at the start. It may be mentioned that a low white cell count at the start is not a contraindication to the use of sulfonamides. Dameshek and Wolfson⁴¹ treated two patients with severe agranulocytosis with large doses of sulfathiazole in the endeavor to control the sepsis, with indications that the drug may have played a part in the recovery which ensued.

Animal experiments⁴² indicate that all members of the sulfonamide group are toxic to the central nervous system, although some are less so than others. Sulfanilamide seems to be less toxic than several of its derivatives, including sulfathiazole. The repeated administration of the sulfonamides seems to sensitize the nervous system. The neurotoxic action is more pronounced in disease of the central nervous system. Among the toxic symptoms seen in man are headaches, dizziness, depression, confusion, aphasia, stammering, toxic psychosis, meningeal symptoms, blindness, convulsions, myelitis, and optic neuritis. Peripheral neuritis with sensory and motor disturbances is sometimes seen. Nausea, vomiting and diarrhea are apparently of central origin. When the milder symptoms occur, the course may be interrupted for a few doses, or the size of the dose reduced. In the more severe forms it needs to be discontinued.

Choice: Concerning the choice of sulfonamides for the treatment of any specific infection, opinion is not unanimous. The early observations that pneumonia was not very satisfactorily controlled with sulfanilamide have received support from subsequent experience, and at the present time the pneumococcic infections are treated almost exclusively with the heterocyclic derivatives of sulfanilamide, namely, sulfapyridine, sulfathiazole and sulfadiazine. The results with sulfanilamide in the treatment of gonorrhea have been, on the whole, striking, but the repeated finding of cases of gonorrhea vigorously but unsuccessfully treated with sulfanilamide which were promptly cured by an essentially similar plan of treatment with sulfapyridine⁴³ suggested that the heterocyclic derivatives might be more efficacious in this disease as well. The observation that gonococci fairly rapidly acquire resistance when exposed to increas-

ing concentrations of sulfanilamide but retain their sensitiveness when treated under the same conditions with sulfathiazole⁴⁴ directed attention to the possibility that sulfathiazole may deserve the first place. More recently, a very careful study from the Brady Institute37 showed that sulfadiazine is probably the most efficacious member of the sulfonamide group in use in this country for the treatment of gonorrhea. A course of treatment with a daily dose of 4 grams for a period of about ten days was found to effect a complete cure in about 95 per cent of the cases. Some of the earlier observations with sulfathiazole suggested that it might be the drug of choice in staphylococcus infections. There seems to be little doubt of its superiority over sulfanilamide, but its position in relation to the other heterocyclic sulfonamides remains to be established. There seems to be some doubt concerning sulfathiazole in any form of meningitis by reason of the fact that little of this drug enters the spinal fluid. This fact does not finally settle the question, however, since the essential action in the control of meningitis may prove to be that of the drug in the circulation rather than in the spinal fluid.

The final word regarding the choice of sulfonamides in the fifty-odd infections in which they are found useful is not yet possible with the available experience. There is, however, competent opinion to the effect that among the sulfonamides in common use in this country at the present time, sulfadiazine serves all the needs of systemic sulfonamide therapy as satisfactorily as any other, surpasses them in some infections and is, by and large, freer of toxic effects.

Drug-fastness: The problem of drug-fastness in relation to the sulf-onamides is receiving increasing attention in the past few years. 44-53 Resistance to the sulfonamides seems to be a characteristic of the strain of organism. What factors are responsible for the natural resistance of bacteria to these agents are not yet known.

There is another aspect of the problem of resistance, namely, the fact that certain organisms are able to acquire resistance if exposed to sublethal doses of this group of drugs. Among the organisms for which this has been demonstrated are included the pneumococcus, the gonococcus, the staphylococcus, and the Escherichia coli. The acquisition of tolerance by an organism when it is cultivated in a medium in which the concentration of a sulfonamide is progressively increased seems, therefore, to be a fairly general characteristic. It applies not only to bacteria exposed to sublethal concentrations of the drug *in vitro*, but to those similarly ex-

posed in vivo in the course of an infection. A very high degree of resistance may be acquired in this way, so that 10 times as much of the drug may be needed subsequently to produce a bacteriostatic effect.44 The acquired tolerance can be demonstrated not only by the greater concentration of the drug necessary to inhibit its growth in a culture, but by the fact that the drug in the customary doses fails to cure an animal infected with this organism.53 The drug-fastness may, under certain conditions, develop very rapidly, as soon as three days after the onset of treatment.47 It may last a year or longer.49 Not all organisms or strains are capable of acquiring resistance to all sulfonamides. For example, in one series of observations44 strains of the gonococcus readily acquired a tolerance to sulfanilamide, but were incapable of acquiring a tolerance to sulfathiazole in a similar type of experiment. In some cases, cross-tolerance has been demonstrated. Thus, for example, in one observation in which the staphylococcus of an infected patient had acquired a tolerance to sulfathiazole as the result of treatment with this drug, it was found that the tolerance also extended to sulfapyridine and sulfadiazine.⁵² In some cases, however, cross-tolerance does not occur, or occurs only in one direction. In one set of experiments⁵¹ it was shown that the gonococcus which had acquired tolerance to sulfapyridine was also tolerant to sulfanilamide, whereas when the gonococcus had acquired tolerance to sulfanilamide, it remained normally sensitive to sulfapyridine.

The mechanism by which microörganisms exposed to sulfonamides acquire a tolerance to their bacteriostatic action is not known. It may indeed be the same mechanism which is known to apply to other drugs, namely, that exposure of a population of cells to low concentrations of a drug results in the destruction of the most susceptible members and the survival of the fittest.

There are many practical questions which are directly related to the problem of tolerance, but which at the moment can not be answered. If a case of pneumonia or gonorrhea fails to respond to one of the sulf-onamides fairly promptly, should one turn to another member of the group in the hope of avoiding the establishment of a tolerant strain which may then fail to respond to others? If so, when should it be done, and to which member of the group should one turn? The matter of dosage bears on this problem. It has been suggested that sulfonamide treatment should be carried out very vigorously and with large doses in order to insure rapid destruction of the organisms, ⁴⁶ in the hope of avoid-

ing the development of drug-fastness by subeffective concentrations. The widespread use of small doses of sulfonamides in the case of minor infections such as colds, in which no satisfactory proof of value exists, may well serve as a means of cultivating carriers of sulfonamide-resistant strains. The dissemination of strains of organisms which have acquired a fastness to the sulfonamides carries implications of far reaching importance to the public health. Explorations in this field have hardly scratched the surface.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



MARCH, 1943

ADDRESS OF THE RETIRING PRESIDENT

MALCOLM GOODRIDGE*

dress I confessed to a feeling of my inadequacy to meet the standards set by my illustrious predecessors in office.

What I did not fully appreciate at that time was that I had been made the titular head of an altogether surprising organization. I would have been spared my solicitude could I have realized how soon I was to be absorbed by its smooth functioning machinery. In every department I was to find friendliness and efficiency.

As one contemplates the history of The New York Academy of Medicine one can, without stretching one's imagination too much, divide the story into four fairly distinct chapters. Chapter One would include that period dating from the adoption of the original constitution on January 6th, 1847 and ending with the occupancy of its first home in 1875. Chapter Two would comprise the years between 1875 and 1890, the latter date representing the opening of the first building actually constructed to meet its growing needs. Chapter Three is most important because it tells the story of the early days of what might be called the modern phase of our development. It begins in 1890 and continues for over thirty years. It is my conviction that one of the most far-reaching undertakings in the Academy's long history occurred in this period.

^{*} Delivered January 7, 1943 at the Annual Meeting of The New York Academy of Medicine.

namely, the formation of the Committee on Public Health Relations in 1911. The service which this committee has rendered is told in a small volume entitled "Thirty Years of Community Service 1911-1941." Of the original membership but one is still living, my immediate predecessor in office, a former chairman of the committee and its present presiding officer, Dr. James Alexander Miller.

The Fourth Chapter began in 1924 with the conclusion of an agreement with the Rockefeller Foundation for an extension of the educational activities of the Academy of Medicine. The essential features of the plan were:

- a. A suitable new building
- b. Development of the library
- c. An efficient information service for visiting physicians-American and foreign
- d. A similar information service for the medical profession of Greater New York and vicinity
- e. A development of medical extension activities at the Academy building
- f. Coöperation with hospitals to provide clinics, etc. throughout the city for the profession
- g. Promotion of popular education with regard to preventive medicine
- h. The appointment of a special educational committee of the Academy
- i. A director of educational work on a full-time basis

The Carnegie Corporation very generously provided for the building.

To these two foundations the Academy and the community owe a debt which is difficult to express in words. It is a satisfaction to know however that they feel that we have justified the faith they had in us.

I shall not attempt to develop the story of the current chapter in Academy history. It is sufficient to state that three of our four standing committees had their origin during this era. The Committee on Medical Education in 1927, the Committee on Sections in 1929 and the Committee on Medical Information in 1939.

This fourth chapter is still being written but I am inclined to believe that a new or fifth chapter is about to be initiated.

Just as chapter four was in part a product of World War I, so in

my opinion chapter five will be written as a direct result of the present World War. Social and economic trends will affect every phase of life. Medicine will face a vastly changed world and medicine must take the lead in determining just what its position is to be in the new order or else the initiative will surely pass to those less qualified to act. The Academy of Medicine is essentially a teaching institution with public health forming the basis for its chief interest in this direction.

It is a matter for regret that a feeling seems to exist in some quarters that the Academy of Medicine does not coöperate as it might with the Medical Society of the County of New York. This is due I think to a failure to recognize the fact that while the two organizations have a great deal in common, nevertheless their aims are in some respects quite different.

The Academy of Medicine maintains a public library free to all during certain hours of the day. Around this feature there have been slowly developing for nearly a century certain educational features which have made The New York Academy of Medicine a distinctive and unique organization. Every standing committee of the Academy is interested in some phase of postgraduate medical education.

It is also well to remember that nearly every Fellow of the Academy of Medicine is also a member of the Medical Society of the County of New York. We therefore appreciate and have full understanding of the social and economic problems with which medicine is surrounded. We as individuals are a part of organized medicine.

This Academy of ours is no "roost where emeritus professors and effete men of letters once cocks of the walk could sit in quiet rows while the fighting was going on beneath them," to quote again a portion of a letter written by Oliver Wendell Holmes on the occasion of the opening of the new Academy Building at 17 West 43rd Street. On the contrary you will find us an active body of men and women giving freely of ourselves for the benefit of the public welfare in matters bearing the slightest relationship to its health. After four years as your president surely I am in a position to state that The New York Academy of Medicine wishes to give full coöperation to the Medical Society of the County of New York wherever it may be found that our objectives run parallel.

Another criticism which has been brought to my attention recently concerns the method employed in selecting candidates for Fellowship in

the Academy. The Committee on Admission is nominated by a group of Fellows appointed by the President for that purpose. Four men are elected each year to serve a term of three years. Thus this committee consists of twelve Fellows duly elected by the Academy at annual elections. During my tenure of office I have attended most of the monthly meetings of the Admission Committee and I have been greatly impressed by the serious consideration given to each candidate for Fellowship. As Academy prestige has increased in the last twenty-five years the qualifications for Fellowship have also undergone change. We are as interested in keeping unqualified candidates out of Academy Fellowship as we are in electing candidates with satisfactory background.

The Committee on Admission represents a cross section of the highest ideals in the medical profession and I can assure you I am as satisfied with the rules under which this committee functions as I am with the way these rules are put into effect.

It would not be possible for me with the time at my disposal to relate more than a small fraction of the activities of the Academy during the past year.

The Library Committee continues to maintain the library of the Academy in a high state of efficiency in spite of the war. Its records have been protected by microfilming. Its rare books are not only covered by war damage insurance but steps have been taken to give physical protection to these irreplacable treasures. We continue to serve more readers than any other medical library on this hemisphere and possibly more than any other medical library in the world at the present time. We are greatly in need of more stack room and work space but these cannot be furnished until we have finished with the Axis powers.

The Committee on Public Health Relations is a civic institution in its own right. During the past year it has released for publication a large and comprehensive volume entitled "Preventive Medicine in Modern Practice."

I would invite you to read the small monograph entitled "Thirty Years of Community Service 1911-1941," if you would familiarize yourselves with the variety and importance of the services rendered in the past by this committee.

The Committee on Medical Education conducted for the Academy a highly successful Graduate Fortnight in spite of the war and an anticipated reduced attendance and I quote from the report of the Director,

"At no time during the fifteen years in which these meetings have been held has the Fortnight Committee more richly deserved the appreciation of the Academy Fellowship and the medical profession at large." The exhibit this year was especially rich in material and reflected great credit on the committee under whose supervision it was assembled. Few of us appreciate how much we owe the members of this Committee on Education for the time and thought expended by them in giving us such lectures as we are privileged to hear on Wednesday and Friday afternoons and for the splendid programs provided for the Stated Meetings of the Academy.

An arrangement has been made by this committee which will increase the circulation of the Spanish and Portuguese language medical journal, America Clinica, so that it will reach fifty-two thousand Latin-American practitioners.

The Committee on Medical Information has coöperated with the Town Hall in repeating six lectures on contemporary medicine. At the request of the Department of Education and Superintendents of Schools thirty lectures for teachers were arranged on the subject "Child Health in War Time Conditions." The third annual one day Health Conference was conducted by the committee and the transactions of the second annual conference were published. This committee also published a "Study of Radio Broadcasting" made under a fellowship obtained from the Rockefeller Foundation, Division of Humanities. The Laity Lectures continue to fill a most important place in our scheme of things. The seventh volume is about to be published. I commend it to you without reservation.

The Committee on Sections has been completely reorganized in the past two years under the guidance of a special committee appointed by direction of the Council.

The war has taken over fifteen per cent of our Fellows into the various services of the country. This has meant not only serious loss in personnel from the staff and the standing committees but also a considerable loss in income from dues. However, the slack has been taken up by those who for one reason or another have been obliged to remain at home.

The special committee composed of laymen and Fellows who have worked so faithfully to give the public an understanding of what your Academy is doing in contributing to its health and welfare deserves a special word of appreciation. Their effort will continue to bear fruit. Let me go back sixty-five years to quote from the presidential address of Dr. Samuel S. Purple on taking the chair as president for a second term on January 18th, 1877. He had the faith that we of our generation are justifying.

"... Does the medical world belong only to the generation which inhabits it? Is it not rather an entailed estate, the income of which the present possessors have the right to enjoy, but not the right to squander or scatter? Are they not in honor bound to preserve the estate intact, institute and develop such permanent improvements as will tend to meet the wants of the generations which will follow? Such are the dictates of a general philanthropy, which emanate from a proper love of mankind, and have the approval of that sound judgment which is strengthened by observation and matured by age. Let not, then, those who have labored for years past to build up here an institution that shall advance the best interests of medicine, and at the same time be as free as possible from the foibles of the profession, become weary in heart; the design is being steadily carried into effect; the end can be surely reached—the object will, by persevering effort, be accomplished."

My task as your President is done. I shall never cease to be grateful to the men I have worked with. I have been carried along on the wave of enthusiasm which pervades our institution, an inheritance from former generations of Fellows. I shall never lose my devotion to the interests of the Academy. I am not going to single out particular individuals on whom to bestow words of praise. It would be a long list and consume much too much time.

I now take great pleasure in presenting to you your new president. He needs no introduction for he has served you long and well as Fellow, Committeeman, Vice President and Chairman of the Board of Trustees. I know of no man better qualified than he both by character and experience to guide you, your President, Dr. Arthur Chace.

THE ACADEMY MEETS THE CHALLENGE OF THE FUTURE*

ARTHUR FREEBORN CHACE

President of The New York Academy of Medicine

Inaugural Address

have considered it an honor to give all his time for two terms to this noble institution, after having devoted years to the advancement of its work. This, Malcolm Good-ridge has done and tonight he ends four years as President of the Academy.

Fortunately for us, it is not an ending but a continuation, for we feel sure that Dr. Goodridge will always share with us our responsibilities and give to us the accumulated wisdom gained during a lifelong service to the Academy, a service which so eminently fitted him for the years as our President.

During this time he has devoted all of his strength and energies to the solving of the many difficult problems which have confronted us. His patient attention to detail, his never-failing faith in the ability of the Academy to meet its ever-increasing burdens, his unselfish devotion and wise leadership will always be an inspiration to those who follow him.

. One cannot contemplate the future either as it may affect the life of an individual or that of an institution without being acutely aware of the great emergency which confronts us individually and collectively. From whatever vantage point we survey the effects of the great storm now sweeping the world we cannot escape the whisperings of anxiety nor deny the imminence of danger. Civilization, even all that the Academy holds most valuable, is threatened with well-organized destruction by men who have wilfully and purposely reverted to barbarism.

Delivered January 7, 1943 at the Annual Meeting of The New York Academy of Medicine.

In Paris, Louvain, Warsaw and in London, libraries have been pillaged or lie in ruins. Books, the very lighthouses of our profession, by which we can steer our course true into the future, have been piled in heaps and burned. In Europe the free interchange of ideas and discoveries, through which science has grown great, is no longer possible.

We cannot hope to penetrate even lightly the mist of the future without casting upon it that illumination which can be gained through the contemplation of the past and the present in historical perspective. The New York Academy of Medicine is now in its 96th year. During these years it has confronted and surmounted many crises. It has shared in the destinies of our people and our country and has, through its constructive work, helped to shape the issues of the years.

The Academy not only survived the internecine strife of the Civil War which broke out shortly after its creation; the trials of the long Reconstruction period and the ordeals of the last World War, but has emerged from these tests richer by the experience and stronger by the trials. This was possible because of the far-seeing wisdom of its leaders and the faith of its fellowship. Both recognized that virile life ever necessitates, as Herbert Spencer so aptly phrased it, the adjustment of inner relations to outer circumstances. The Academy has never wavered in its devotion to its objectives which were the reasons for its creation; to foster the science of medicine and to maintain the highest ideals in its practice. Wisely, however, the ways in which the Academy has pursued these objectives have changed with time. They have grown in scope and in complexity even as did our science and our social and economic existence.

The Academy has undergone a series of revolutionary progressions. In the earliest years of its existence, it was chiefly devoted to the collection of a library where men might read and learn. Then, as the need for discussion in common impressed itself upon the fellowship, there developed a strong drive for the procurement of a permanent home for the Academy. Still later, and that brings us down to the beginning of the present century, as our community grew in complexity and as our science developed infinitely, it became evident that precious as was our library and useful our meeting halls, they could not serve to fulfill the growing obligations of medicine to society. In that way, thirty-one years ago, there came into being the Public Health Relations Committee, eighteen years ago the Committee on Medical Education, and more

recently the Committee on Medical Information.

These developments and achievements so briefly summarized, were not realized without great effort nor without contest even in our own fellowship; "the adjustment of their inner relations to outer circumstances" is never an easy accomplishment. Yet that they were achieved is witnessed in our history and with what profound benefit to the medical profession and to the public, is attested by all. The Academy will continue to collect, preserve, distribute, and advance all that is best in medical skill. For, in the words of Hippocrates, familiar to you all: "The physician must know what his predecessors have known, if he does not wish to deceive both himself and others."

What is there, then, in the knowledge of our predecessors which will help the Academy to meet not only the challenge of the present but also the still greater challenge of the future? More than two thousand years ago Heraclitus laid down what he believed to be one of the fundamental laws of the universe. "There is nothing permanent," he said, "except change." Certainly science has found little to disprove that assertion and much to confirm it.

Some medical men, influenced by Darwin, have tended to believe that, through the elimination of the unfit, the forces of Nature move continuously upward and onward. They see now what they had almost forgotten, that during certain periods the body politic, like the body human, may stagnate—even retrogress. The undesirable and destructive elements are in the ascendant and although change never for a moment ceases, it is not ipso facto to be assumed that the change is for the better. "All that is buman," said Gibbon, "must retrograde if it do not advance."

This then, I humbly submit, is the beginning of wisdom for the Academy in these perilous times. But despite the fact that half the world is in flames, we do not have to retrogress. It is our sacred duty. our inescapable destiny, to advance, eyes open, into the future, there to meet whatever challenge life shall hold.

Medicine being of the web and woof of our social life shares in all the changes and also in the anxiety with which all mankind faces the future. Forthwith, however, some of this anxiety can be dissipated in the realization that whatever else betides the world, as long as there are men on this earth, there will be illness among them and as long as men are ill they will be in need of the best care that medicine can afford them and will want that care administered to them in the best tradi-

tions in which the Art is to be practiced.

In this we have much to fortify us. In the last seventy years medicine has achieved more scientifically than it had in the rest of recorded time. More freely than ever before "the never-idle workshop of Nature" has been yielding up its secrets to man. To the successful use of the sulfonamides has been added the discovery of the most dynamic vitamin, Biotin. In the past few years the hypothesis of the atomic theory has been strengthened by the splitting of the atom. In the case of uranium the amount of dynamic energy thus released has actually been measured. We are on the threshold of solving many riddles, among which it seems safe to place such virus diseases as infantile paralysis, the common cold and the newer form of virus pneumonia.

But here we are confronted by what appears to be another universal law that behind each advance of science lurks some new and concomitant problem. No sooner does the profession feel reasonably confident that the cure of pneumonia has been found than a new, virus-type form appears. It does not respond to the new treatment. Medicine must then immediately institute new research, hopefully employing gramacidin and penicillin.

The United States is fortunate today in that many of the greatest scientists of the modern world have gathered here under the standard of liberty and will join our scientists in this basic research.

Life expectancy at birth has during the past twenty years been extended by at least ten years through the work of modern science. The problem thereby created is the treatment of the largely increased illnesses associated with old age. The development of the specialty of Geriatrics is a pressing problem wherein the Academy must forge ahead in its educational program, fitting physicians to meet this demand, else we would not uphold Browning in his plea:

"Grow old along with me— The best is yet to be!"

Physical science, however, has advanced much more rapidly than have our social sciences, and to this lag may be charged many of the problems that are facing us today. Our biological, chemical and physical discoveries have far outrun our social and economic adjustments and the war demands have completely thrown society out of gear. In no other branch of science as in medicine have its discoveries been so quickly, and at so little cost, put at the disposal of the public; but still

it is not enough. In this lies the Academy's opportunity and obligation to educate the medical profession for their proper use and the laity for proper coöperation.

The approach of the Academy to medicine has always been—and must continue to be—through the individual patient. This is, in many respects, the more difficult way. But for society as a whole it is, infinitely, the surer way.

It is also, I believe, the future way. Two recent portents will confirm us here: Lord Nuffield recently endowed for a period of ten years, the Institute of Social Medicine at Oxford—an interesting and significant event which has received too scant public notice. Let me quote the exact words of the announcement of the Institute's objectives:

"To investigate the influence of social genetic, environmental and domestic factors on the incidence of human disease and disability.

"To seek and promote measures, other than those usually employed in the practice of remedial medicine, for the protection of the individual and of the community against such forces as interfere with the full development and maintenance of man's mental and physical capacity."

In the same spirit, but with a somewhat different objective, should be mentioned the creation of the Nutrition Foundation by a group of food and other, closely related manufacturers. This foundation has assigned a fund of a million and a half dollars to support a five-year program in the application of the science of nutrition.

We have, apparently, some companionship in going out to meet this challenge. On the one hand we have a philanthropic University foundation; on the other a purely industrial foundation, both supported by large sums of money and both devoted to the application of the medical sciences to the improvement of the well-being of man.

We have an ally more precious still. Never before has the public been more interested in the scientific and the sociological aspects of medicine. No "social architect" can meet this hunger because it is not a hunger for more social theories. It is rather a hunger for established facts, truthfully correlated and interpreted in the impartial light of science. Society's ills, as the public instinctively feels, are not going to be cured by the anodyne of wishful thinking. They are beginning to see that the first step is the same as in the treatment of disease in an individual patient. We must clearly define the disorder, its symptoms and its probable causes. Then and then only may we recommend such

remedies, such changes in environment, as will remove the morbid manifestations by eliminating their causes.

It would be presumptuous for any man to pretend that, standing in the midst of the storm, he can diagnose with full accuracy the nature of society's present global difficulties, their causes and their cure. Yet the medical profession, standing on the solid base of known fact and trained, as it is, to maintain calm in the face of any disaster, will be able assuredly to make a worthwhile contribution.

The humanitarians of the last century, the Chadwicks and the Shattucks, could do no more than protest angrily against the degrading circumstances in which so many men labored and lived. But not until modern medicine revealed the microbic, the diet deficiency and other causes of disease, could their socially-righteous indignation be implemented and rendered effective. It is not enough to feel; it is essential also to know.

As long ago as the Seventeenth Century, Shakespeare could have King Lear say,

"Poor naked wretches, wheresoe'er you are,
That bide the pelting of this piteous storm,
How shall your houseless heads and unfed sides,
Your loop'd and windowed raggedness, defend you
From seasons such as these? . . ."

He could ask the question but there was not, at the time, a man, nor any group of men, anywhere in the world who could give answer. They simply did not know.

Today, at least, medicine can offer a clear and valid knowledge on many fronts—fronts which it is our duty to expand. To every segment of man's life, whether it be at home or in the work place, on the battle-field or in the metropolis, medicine has been and is making fundamental contributions in knowledge and in guidance. We have made vast advances on the physical front and some, but not enough, on the psychological front.

I would not add even so much as one to the thousands of definitions of Man. But on the fact that Man is above all a thinking animal, all of us would be in agreement. Part, at least, of the challenge of the future to the Academy, therefore, is that it must think more clearly and deal more thoughtfully not only with man the corporeal being, but also with man the cogitating creature.

Yet here we must be aware of a pitfall which has engulfed so many of our contemporaries. We must not be tempted into drafting a blue-print for salvation; one of those schemes which are compounded out of wishful thinking and the naive belief that given but enough enthusiasm we could—

" conspire
To grasp this sorry Scheme of Things entire,
and then

Re-mould it nearer to the Heart's Desire!"

We need rather to follow the same pattern that serves us when we deal with the ills of man. And in all this we must cleave to that wisest of all therapeutic precautions "above all—to.do no harm."

It must be patent to everyone that much of our difficulty can be charged to the enormous disparity that exists between our scientific and technological advances and our social and economic evolution. In the light of what we know we are woefully backward in what we do. We must then catch up with these advances realizing that the crux of the problem is how this catching-up is to be effected.

To this problem medicine with its vast encompassments can and must make a solid contribution; for medicine can contribute its knowledge to the thinking and planning of the social architects who are ambitious to build the society of tomorrow. Today there is a vast and potent body of medical knowledge that can serve to make the world a better place to live in. For medicine, notably during the present century, has extended its sway far beyond the mere diagnosis and treatment of illness. It has gained precious knowledge about the normal operations of the human body, and, no less significantly, the normal, as well as the abnormal operations of the human mind and psyche. Today, better than at any time in the history of mankind, we know how to promote and to conserve human well-being physically, mentally and emotionally.

We call in witness of this the enormous strides that have been made in the specialties of nutrition and psychiatry. In place of those truly fantastic speculations about man and his social relations, initiated by Rousseau and since elaborated by many different schools of thought, medicine today offers a much clearer and infinitely more valid body of knowledge on the psychological mainsprings of human behavior. It is no accident that in the world strife of today this knowledge has been enlisted in the propaganda battle between the warring nations.

It may seem that we have wandered far from the title of our paper, The Academy Meets the Challenge of the Future, but in substance we have not. For in all those "affairs of today and tomorrow" which have been described, those which are in substance "the challenge of the future," the Academy has an important role to play. For the "social architects" will not entirely and on their own initiative come begging for the guidance and instruction that medicine affords.

It is, therefore, necessary that medicine should exercise its influence actively, not with the aggression of a "pressure group" but rather with that positiveness which is warranted by its knowledge. This is no new function, nor yet a novel role for the Academy. For more than three decades the Academy has through its Committee on Public Health Relations, through its Committee on Medical Education and more lately through its Committee on Medical Information, played an ever-increasing role in dealing with problems of public policy.

We are resolved to continue and to intensify these activities. More specifically, though without elaborating the details too largely, we at the Academy propose to institute in the immediate future, through our standing committees and through such special committees as will be required, careful and thorough-going studies of the trends and the indicated future developments in medicine and in communal and public health. We propose to scrutinize carefully the proposals and plans for the post-war world that are formulated by responsible and authoritative agencies. We intend to do this so that we may be fully informed and in a position to contribute effectively to such services as we may be ultimately called on to render. It is likewise our intention to devote thought and consideration to the more immediate problems that confront us in the medical world, to those that stem from the rapid changes that are taking place in the undergraduate education of the physician, from the reorganization and the administrative changes of the voluntary. hospitals that are dictated by the curtailment of financial support, from the withdrawal of so many physicians from civil practice to military service, from the relocations of populations, and we must also devote our attention to those various health problems that issue from food and fuel rationing, from the intensification of our industrial efforts, and from the increased participation of women in war work.

Now once again, with pressing urgency, demands are made upon us. We are meeting—we must continue to meet—these demands. Civilian

Defense Units must be kept up to date. Catastrophe Teams must be kept continually on the alert. Plans must be perfected for the emotional and physical rehabilitation of men returning from the war. The Refresher Courses must be given with increasing intensity. Yes, many a specialist must now reverse his steps and, with eagerness, set out to become the improved counterpart of the Horse and Buggy Doctor.

If only one-half of the former number of active doctors remains in New York to look after the entire problem of public and private health, then men over forty must renew their youth in vastly-increased service to the community.

The Academy must add to its responsibilities without relinquishing a single one of its activities in the State or Nation.

These, then, are the challenges of the future. These, we must go forth to meet. The fellows of this great institution must be not only defenders of the noble traditions which they have inherited, they must also strike out fearlessly into the unknown. We must purpose to be more than guardians. We must resolve—

"To follow knowledge like a sinking star Beyond the utmost bound of human thought."

I would not have you believe that ours is an easy task. Encompassed about on all sides by destruction, by change and by manifold anxieties we must nevertheless continue—

"To strive, to seek, to find, and not to yield."

We must so live and so achieve that, fifty years hence, members of this august body, looking back, will say, "Those were great years in the Academy's history. In troublous times, they held the torch aloft."

When others falter, or lose the way, the Academy must—the Academy will—point the way and define the path which the medical profession should follow. Physicians, true to their calling, will be inspired by the difficulties and burdens that await them and with one accord give unsparingly of themselves. For, as Hippocrates truly said, "Wherever the Art of Medicine is loved, there also is love of bumanity."

We live in a changing world. We live in a world at war. We must realize now, more than ever before, that—

And we must take the current when it serves.

"On such a full sea are we now afloat.

Or lose our venture."

A RESUMÉ OF THE PRINCIPAL DIAGNOSTIC FEATURES OF SUBDURAL HEMATOMA*

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matic origin, occurring with increasing frequency in the mechanized era in which we live, producing symptoms at variable periods following injury and should be entertained as a possible complication of every craniocerebral trauma however trivial the accident may have seemed. As holds true for the advancements of our knowledge regarding any particular clinical entity, a few outstanding contributions concerning subdural hematoma have been responsible for the progress that has been made in the treatment of patients with this pathological process. It was in 1857 that Virchow1 reviewed the previously proposed concepts relative to encapsulated hemorrhages in the subdural space and set forth his own thoughts regarding the pathogenesis of this lesion. This article appears to have influenced medical thinking for the next fifty years. In any event during this period it was quite generally held that blood clots disclosed in the cerebral subdural space were chronic in character and existed for the most part in idiots, the senile and the insane. In 1905 Bowen² presented a study of 72 cases of subdural hematoma reported in the literature between 1870 and 1900 and adduced evidence indicating that there was a causal relationship between trauma and this lesion. This excellent presentation of the subject remained relatively obscure and it was not until twenty years later that Putnam and Cushing3 in 1925 focused the attention of the present generation of American surgeons on a pathological state that could be cured by appropriate surgical measures. Beginning in 1934 Munro⁴ contributed a series of articles dealing with the pathogenesis, the diagnosis and the surgical treatment of the varied subdural collections that complicate craniocerebral injuries. His work has been important in that many problems relative to pathogenesis have been studied in considerable detail. Contributions by

^{*} Read October 13, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

Frazier,⁵ Peet and Kahn,⁶ Jelsma,⁷ Ingraham and Heyl,⁸ Kaplan,⁹ Kunkel and Dandy,¹⁰ Leary¹¹ and others have advanced our knowledge concerning this lesion.

In striking contrast to the ideas held during the nineteenth century it is now well substantiated that trauma to the head is by far the most frequent etiological factor in the production of subdural hematoma, however, these lesions may be the result of spontaneous hemorrhage. I have observed examples of bleeding into the subdural space from cortical vessels implicated by a metastatic tumor of the brain, from ruptured cerebral aneurysms, from an arteriovenous malformation on the surface of the brain and from the region of subcortical abscesses. In most instances a moderately severe traumatic cerebral insult has been sustained with resultant contusion-laceration of a temporal and/or under-surface of a frontal lobe. Bleeding from lacerated vessels in one or the other of these damaged areas collects in the subdural space. Or a vein crossing from the cerebral cortex to the dura or leading into one of the dural sinuses may be torn with the production of a large blood clot. In some it is impossible even at autopsy to identify the source of the hemorrhage. Recently established collections in the subdural space may consist

of solid blood clots, blood admixed with cerebrospinal fluid or xantho-chromic fluid in considerable quantity, the so-called subdural hydroma. Slowly a membrane is formed about the collection, that portion of the capsule on the dural side becoming relatively thick and quite vascular, whereas the membrane adjacent to the arachnoid is thin and devoid of prominent blood capillaries. The accumulated evidence indicates that coagulated blood usually undergoes liquefaction and, as pointed out by Gardner,12 adjacent fluid (cerebrospinal) is drawn into the subdural collection producing an increase in the size of the intracranial mass. The clinical course of many patients suggests that the subdural mass may enlarge several days, weeks or sometimes months after the accident or, at any rate, symptoms put in their appearance at these late dates. Occasionally the clot is invaded by fibroblastic elements with a resultant organized mass. Yet patients in whom this has occurred may manifest the same delayed symptomatology as observed in those with encapsulated fluid collections. It seems unlikely that an organized blood clot could expand within a few days after being relatively quiescent for many weeks. Alterations in cerebral circulation in the vicinity of either an organized blood clot or the chronically encapsulated fluid collections

are more likely the explanation for the symptoms. In support of this concept specimens obtained at autopsy have shown obvious edema of the brain adjacent to an encapsulated fluid hematoma. This local edema could be logically assigned as the cause of the clinical signs which had been demonstrable. The organized blood clots and the more commonly encountered encapsulated liquid subdural collections are the lesions that have attracted the attention of neurological surgeons and concerning which excellent discussions have been recorded. These collections are not infrequently disclosed at operation, under the mistaken diagnosis of brain tumor. They are found in patients who have survived a mild to moderately severe head injury which in many instances has long since been forgotten. They have been termed chronic subdural hematoma, a designation entirely consistent with the duration of the lesion, however, the term should not be used to imply that this syndrome has a separate and distinct pathogenesis from the so-called acute subdural hematoma. The chronic state is merely a latent variant of the acute. Moreover the patients with chronic collections present symptoms and signs that are readily interpreted as representing a space-taking mass in the head and if not localizable by clinical findings, their position can be accurately determined by Dandy's method of ventriculography. The mortality from operative removal of these chronic lesions should be almost nil, therefore, further discussion concerning this entity need not detain us here.

The acute form and the subacute variety, if terms signifying duration of the lesion are permissible, are the commonest types of subdural hematoma. Some patients with this lesion die within a few hours following injury, some survive for several days in a state of continuous stupor, others rouse from stupor after three or four days only to lapse into coma in the next eight or ten days, and still others less severely injured become oriented two or three days after injury, remain so for two or three weeks albeit complaining of headache, then backslide into a confused state. While it is recognized that the subdural collections associated with these syndromes are often a single complication of a general brain insult and surgical removal may not favorably influence the eventual outcome in some that are severely injured, nevertheless, prompt recognition of the probability of such a lesion, the employment of appropriate diagnostic measures and the execution of judicious surgery will save many who otherwise would succumb.

During the past eight years there were admitted to the Kings County and Brooklyn hospitals 18,272 patients with varied types of craniocere-bral injuries. Among these there were 289 instances of subdural hematoma. A study of 143 of these (five year period) has been previously reported. Experiences with the entire group of 289 cases has led to the conclusion that an accurate diagnosis is seldom possible from the clinical features alone. In by far the majority of instances there were associated intrinsic brain lesions productive of abnormal physical signs which served to confuse the diagnostic issues. There are, however, a few clinical observations that are significant and are indispensable aids in arriving at a working diagnosis. These are: (1) the external evidence of trauma to the head and an estimation of the area receiving the maximum blow, (2) the state of consciousness, (3) the condition of the pupils, especially inequality, (4) weakness of an extremity or extremities of one side and (5) the status of the superficial and deep reflexes. Aside from the verification that a blow to the head has been sustained, the observations relative to the conscious state are most important. A short period of drowsiness or stupor, the consequence of the initial insult, followed by enduring orientation is seldom associated with subdural hematoma. However, a period of a day or two of confusion or drowsiness followed by several days to weeks of relative lucidity, during which the patient's intellect is mildly blunted, and then the supervention of progressive drowsiness to stupor, is highly suggestive of a subdural collection. Profound stupor following a craniocerebral injury, with or without physical signs indicative of a focal lesion of the brain, that continues longer than 48 to 60 hours also indicates that all is not well and the patient is in need of further diagnostic and therapeutic measures.

The condition of the pupils, especially inequality, has not been found to be as helpful a guide as reported by some. The pupils were recorded as unequal in 46 per cent, or 132 cases, of the series. In 29 per cent of these 132 cases, the larger pupil was on the opposite side to the subdural collection. In only 11 per cent was there found an unequivocal widely dilated pupil on the same side as the lesion. It is therefore evident that one may be misguided by attaching undue importance to the presence of unequal pupils.

Weakness of an extremity or extremities of one side was observed in 166 of the series. The hemiparesis was present on the same side as the subdural hematoma in 64 of these. In other words, 22 per cent of the entire series of 289 cases had weakness of the extremities on the same side as the subdural hematoma. The presence of motor weakness of the extremities of one side following a craniocerebral injury does not necessarily indicate that the cerebral hemisphere of the side opposite the weakness is being compressed or otherwise functionally altered by a blood clot. If a hemiparesis be demonstrable, however, the possibility of an intracranial hematoma should be entertained and the diagnosis of such a lesion be established or excluded by small multiple cranial openings and/or ventriculography.

The reflexes, both superficial and tendon, are frequently found to be abolished shortly after a moderate or severe craniocerebral trauma. Babinski's sign may be present bilaterally. After recovery from the immediate effects of the insult the tendon reflexes may be obtained, although such bizarre reflex findings are frequently present that interpretation is difficult. In truth, observations relative to semi-purposeful or random movements of an extremity or extremities are more helpful in estimating disturbances in neural mechanisms than are refined tests.

Records of the pulse rate, respiratory rate, blood pressure and the cerebrospinal fluid pressure and its characteristics should be kept, but these singly or in combination are not to be considered as reliable indices for therapy. They are only a part of the entire clinical picture and are to be evaluated accordingly.

From this abbreviated account it would seem that time honored clinical findings derived from physical examination are wholly unreliable. In many instances this may be true and the evidence obtained from ventriculographic examination supersedes all the other observations. Although this form of examination is many times an indispensable aid in establishing or excluding the presence of a subdural hematoma or other intracranial blood clots, one does not inject air into the cerebral ventricles of every patient who is in an unconscious state. It is still important to arrive at a reasonable clinical diagnosis before subjecting the seriously injured to an operative procedure however minimal. Familiarity with the clinicopathological syndromes that are commonly encountered is therefore essential for differential diagnosis.

As previously alluded to, multiplicity of cerebral lesions in the same patient is one of the greatest obstacles in identifying the presence of a sizable blood clot that should be surgically removed. It is often impossizable blood clot that should be surgically removed.

sible to assign with certainty the etiological factors to obviously abnormal neurological states. The clinical features of the common syndromes may be elaborated upon to advantage. There should be no question regarding the therapeutic course to pursue in any patient who has sustained a cerebral insult with or without immediate loss of consciousness followed by a period of relative lucidity and this superseded by drowsiness, stupor and deepening coma. 'Tis true that exceptions are encountered; however, under these conditions the advent of drowsiness with or without focal signs is the signal for prompt surgical intervention. This is the story of slow arterial bleeding in the intracranial cavity. The blood clot may be located epidurally, subdurally or within the brain itself. The abnormal physical findings are often insufficient to localize the lesion with precision, therefore ventriculography is essential before any operative procedure is carried out. It is unwise and unsafe to attempt the removal of hematomas, be they epidural, subdural or intracerebral, through a traditional subtemporal decompression opening. If the subdural collection is not entirely liquid and cannot be evacuated through two small cranial openings then it is preferable to utilize a small bone flap made over the site of the lesion as demonstrated by the air studies.

There is a second clinical syndrome that calls for prompt and precise diagnosis followed by appropriate surgery according to indications. The following is an illustrative story: A patient who has sustained a moderately severe craniocerebral injury is admitted to the hospital shortly after accident. He is drowsy, disoriented and non-coöperative. The pupils are equal, the extremities are moved about equally well and no abnormalities in reflexes are demonstrable. Slowly over a period of eight to twelve hours stupor supervenes and one pupil is found to be slightly larger than its fellow. Pinching the pectoral muscle border or application of other painful stimuli evokes acceleration and increased depth of respirations and transitory skeletal muscle hypertonicity with all the extremities in a fully extended and rigid posture. Shortly, this rigid state, or so-called decerebrate rigidity, becomes almost continuous, the breathing is labored and forceful, the jaw set and the facial muscles contracted, simulating somewhat the sardonic grin of tetanus. The temperature rises and the pulse becomes accelerated. The skin is flushed, at first dry and hot, later the patient is bathed in his own sweat. Such a course of clinical events has been observed in association with a wide variety of lesions: epidural, subdural, intracerebral or intraventricular hemorrhage, diffuse small hemorrhages throughout both cerebral hemispheres often associated with contusion/laceration of one or both frontotemporal regions, and/or hemorrhages in the upper part of the hind brain. The pertinent point relative to the present discussion is that a large subdural hematoma may be the cause of this clinical syndrome. While it is known that the decerebrate or decorticate attitude, regardless of the causative factor, is a bad prognostic sign, nevertheless, we have had a number of recoveries following the removal of large blood clots in patients manifesting these clinical features. It has been observed that inequality of pupils and the decerebrate attitude are more commonly associated with large supratentorial hematomas than are equally constricted pupils and the decerebrate attitude which are not infrequently found in association with hemorrhage within the upper hind brain. In all events the appearance of decerebrate rigidity in any patient who has sustained a head injury calls for ventriculographic examination unless a surface hematoma be disclosed in the making of bilateral openings for purposes of this examination. Further surgery is carried out in accordance with the information derived by inspection through the cranial burr openings and/or the aerographic study.

The third group of patients with craniocerebral trauma complicated by subdural collections comprise those that remain confused, drowsy or stuporous from the time of injury until the hematoma is surgically removed and/or death ensues. The obvious lesions of the brain disclosed in those that come to autopsy are single or multiple surface contusions or lacerations with regional edema. As previously stated a surface vessel, often a vein, has been torn at the site of the cerebral contusion and bleeding has occurred into the subdural space. Approximately twothirds of all subdural hematomas are the result of this type of lesion. The clinical course of patients so injured is quite variable, dependent no doubt on the pathophysiological alterations within the brain itself. At least the marked changes in temperature, pulse rate, respiration, etc. suggest primary dysfunctions of the vegetative system. On the somatic side, hemiparesis or hemiplegia are not uncommon. Here again the exact role played by the subdural collection in the production of motor weakness of the extremities is difficult of evaluation. Often a lesion within the brain appears to be the more important. Be this as it may, patients severely injured frequently die within twelve to thirty-six hours follow-

CHART I

| Number of subdural hematomas operated | 227 |
|--|-----|
| Number of subdural hematomas non-operated but verified at autopsy. | 62 |
| Total number of subdural hematomas (operated and non-operated) | 289 |

| Time elapsed between Injury and Operation | Total | Recovered | Died | Mortality |
|--|-------|-----------|------|-----------|
| 2 to 24 hours | 51 | 9 | 42 | 82% |
| 1 to 7 days | 65 | 34 | 31 | 48% |
| 7 to 14 days | 48 | 36 | 12 | 25% |
| 14 to 21 days | 33 | 26 | 7 | 21% |
| 21 to 28 days | 11 | 8 | 3* | 27% |
| Over 28 days . | 19 | 17 | 2 | 11% |
| Totals | 227 | 130 | 97 | 42% |

^{*} One of these had a subdural collection associated with multiple metastatic foci of infection in the brain.

ing the accident. Surgical removal of a subdural hematoma carried out during this critical period seldom alters the situation in a favorable manner. In fact we have come to believe that the removal of hematomas during the first twenty-four hours after injury is seldom justifiable. Chart I clearly illustrates the reasons for this position.

This chart shows the progressive decrease in the mortality rate following operation in those that were successfully carried through the critical period after injury. The sixty-two patients who died without operation represent those admitted to the hospital in a moribund state. Many of the patients from whom subdural hematomas were removed during the 48 hour period following injury presented evidence of severe brain damage. Among these, operation was a "last-resort" affair in many instances.

If the employment of supportive measures will not tide the patient over this critical period, then little should be expected from surgical intervention. Those less seriously injured usually weather the storm. However, if after a few days of progressive improvement there ensues drowsiness or untoward alterations in vital signs, the presence of a subdural hematoma should be established or excluded by making multiple small cranial openings and/or ventriculography. If a hematoma is disclosed by these examinations it should be promptly removed regardless of its anatomical position.

SUMMARY

It has been well established that in the majority of instances trauma is the cause of cerebral subdural hematoma. The varied alterations that take place in the size and consistency of many of these blood clots is still not well understood. Furthermore, the role played by cerebral edema adjacent to a chronic encapsulated hematoma in the production of symptoms and signs is also in need of further consideration. The clinical manifestations attending craniocerebral injuries complicated by subdural hematomas are difficult of interpretation. Multiplicity of lesions within the intracranial cavity is the rule rather than the exception. A few clinical syndromes are encountered, however, that suggest the possibility of a subdural collection. Whenever suspicion arises regarding the presence of such a lesion the diagnostic issues should be clarified by multiple small cranial openings and/or ventriculography. Except under circumstances as described the surgical removal of a subdural blood clot during the first 24 to 48 hours following injury is of questionable value. Patients seriously injured should be given supportive treatment during the critical phase of their illness and surgical therapy instituted only after the vital signs indicate a degree of stabilization.

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VIRAL PNEUMONIAS*

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The series of the disease in the majority of cases is unknown, confusion in terminology has arisen.

In the Army Medical Service, the disease is officially called "Primary Atypical Pneumonia, Etiology Unknown" to avoid error, since agents other than filterable viruses may cause a similar syndrome, and it is only surmised that a filterable virus is operative in most of the cases observed. The term is broad, however, and may include any pneumonia not conforming to the typical clinical lobar form. Even the popular term "virus" pneumonia is not specific. It is euphonic, but is as inclusive and as ungrammatic as the term "bacterium" pneumonia would be. The adjective "viral" is preferable. There are many kinds of bacterial pneumonias and perhaps as many of viral pneumonias, judging by the number and variety of filterable agents recently associated with them. Viral pneumonia is therefore a syndrome of which there are many causes. Reviews of the subject were recently published.1,2 It is hoped that eventually, all of the causes will be discovered and simple diagnostic tests will be perfected to enable one to give specific names to the various viral pneumonias as in dealing with the bacterial ones. Some success in this direction has already been attained.

Several authors regard "Viral" pneumonia as a new disease, but the experience of others,³ together with its diverse causation, certainly indicates that it is not. Descriptions of similar disease in medical publications decades old have been pointed out, ^{1,3b} To be sure, such descriptions can be found, but it seems futile to compare them with those of the present because of the emphasis then placed on clinical and pathologic aspects, in contrast with the current etiologic viewpoint. In retrospect it seems most likely that the viral pneumonias were considered as influenzal pneumonia, bronchopneumonia, migratory pneumonia, in-

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terstitial pneumonia4 or capillary bronchiolitis, and that many cases were not recognized as pneumonia at all because of the paucity of physical signs and because roentgenograms were seldom made.

Another point was recently raised as to whether or not "viral" pneumonia, as we now see it, is but a variant of the 1918 influenza, capable of assuming pandemic proportions and of clinical identity with pandemic influenza. It may be, of course, but in all reports thus far published there is a remarkable freedom from complications with pyogenic bacteria which played so fatal a role in the 1918 pandemic, and the mortality rate is nil in otherwise healthy persons. In fact, pneumococci of any type are seldom found in the nasopharynx during "viral" pneumonia, even less often than in healthy persons, 50 per cent of whom are said to be carriers of pneumococci.

Incidence: It may be only a coincidence that "viral" pneumonias sprang into prominence in 1938, after the introduction of sulfapyridine as a curative for pneumococcal pneumonia, but they have without doubt increased both in relative and in actual numbers since then. Several reasons may account for this, named in the order of probability: (1) Their actual increase may be a manifestation of the natural fluctuation in incidence common to many infectious diseases; (2) Diagnosis is made more frequently because of interest in the disease and because of the freer use of roentgenography; and (3) A diminution of the incidence of pneumococcal pneumonia induced naturally and also artificially with chemotherapy emphasizes a relative increase of unusual forms to which little attention has been paid in the past.

In our experience last year2 "viral" pneumonias comprised about 15 per cent of the pneumonias admitted to the hospital; in a Detroit hospitale the proportion was as 6 is to 7, but thus far in the late months of 1942, "viral" pneumonias have outnumbered pneumococcal pneumonias on my service in the ratio of 3 to 1. It was thought that this increase occurred partly because pneumococcal pneumonia is now largely cured at home and that only patients with pneumonia refractory to chemotherapy come to the hospital. It has also been my impression that the undesirable custom of making diagnoses by exclusion is growing. Instead of troubling to determine the causal agent, chemotherapy is often used as a therapeutic test. In one report, the term "sulfonamide resistant pneumonia" was actually used.7

Etiology: The viruses of psittacosis, vaccinia, variola, measles and

influenza were long known to cause forms of viral pneumonia. More recently the viruses of varicella, lymphocytic choriomeningitis, a psittacosis-like disease (ornithosis) and other ones less well defined^{8,9,10} have also been associated with the disease. Furthermore, the viruses of psittacosis and ornithosis have been found to be closely related to those of lymphogranuloma venereum and mouse meningopneumonitis, suggesting that some of these viruses may be widespread in birds and animals, which in turn may serve as sources of infection for Man. Several more viruses implicated in pneumonia have just been added to the list. A virus was isolated from sick cats belonging to a farmer's family afflicted with pneumonia. Evidence suggests that the same virus infected the human patients.15 A similar circumstance was reported by Baker,11 but in this case the causative virus was different, and preliminary studies strongly suggest its relation to the psittacine group. If relationship does exist and if the precedent of nomenclature for the psittacine group is valid, the name "alourosis" may be suggested for this infection in cats. The existence of this virus adds to the fascinating problem of epidemiology concerning the relationship and transference of viruses between birds, animals and Man. The question arises as to whether each of these apparently closely related viruses are descendants of a single parent form modified by adaptation in different hosts, whether one may change into another, if each represents a specific "type" of a genus, analogous with types of pneumococci, and each type selects the host in which it is best fitted to survive, or if they are identical. Indirect evidence already suggests that viruses of this group are implicated in from 1512,16 to 502 per cent of cases of human "viral" pneumonias.

Eaton and his associates¹³ recently succeeded in transmitting and establishing a virus presumably obtained from patients with viral pneumonia in the cotton rat. The evidence of a causal relationship of the viruses to the pneumonia in patients, however, is incomplete because of irregular results of neutralization tests.

General Forms of the Syndrome: According to my experience,² it would seem that the "viral" pneumonias fall into two general groups:

A. As a sporadic, non-seasonal, slightly contagious, systemic disease, with a relatively long incubation period of ten days to two weeks, occurring in isolated instances or in small groups of cases of varying severity, centering around a single source of infection. The epidemic disease in infants described by Adams probably falls into this classification.

In adults, the disease was at first confused⁸ with psittacosis which it strongly resembles. It is probable that the viruses of the composite psittacine group of infections, lymphocytic choriomeningitis and the viruses established in the mongoose and in cotton rats among others yet unknown are operative. The disease appears to be a systemic one, often with splenomegaly and nervous symptoms, in which the lungs are incidentally affected. Manifestations of pulmonary involvement may be delayed for days. This feature has given rise to another undesirable term, "silent bronchopneumonia." The upper part of the respiratory tract is seldom affected to the extent that it is in the other group. In the individual case, however, certain clinical signs and symptoms such as the normal or subnormal leukocyte count, the roentgenographic appearance of the lungs, sweating, unproductive paroxysmal cough, bradycardia, photophobia and the duration are the same as those in the next group.

B. As the severest cases in large epidemics of mild, highly contagious, local disease of the respiratory tract, commonly called colds, grip or influenza, occurring usually in the cold months. The incubation period appears to be short, a matter of one or several days. Generally the disease is indistinguishable from Influenza A or Influenza B, yet it is caused by a different agent or agents, and the three or more specific diseases often occur together in varying proportions in the same epidemic. It seems to be primarily a mild infection of the upper part of the respiratory tract which in the occasional case already affects the lungs or spreads downward to cause pneumonia and severe disease.

If general classification on this broad clinical or epidemiologic basis is correct, a tentative loose arrangement of the various causes of viral pneumonias may be listed as shown in Table I.

It is obvious that further progress in differentiation and classification awaits the discovery of the causative agents in whatever form the syndrome occurs.

Specific Therapy: All observers agree that the sulfonamide compounds have no favorable influence on viral pneumonias. In general, the signs, symptoms and results of laboratory tests of viral pneumonia are distinctive enough to permit quick differentiation from the usual forms of bacterial pneumonia, so that the practice of giving sulfonamides routinely to all patients with pneumonia regardless of the cause is unjustified. It also is unwise to make diagnoses by using sulfonamide compounds as a therapeutic test. In doubtful cases, or when evi-

TABLE I

Sporadic Non Seasonal Forms

Varicella

Vaccinia

Variola

Psittacosis (parrot, parrakeet, etc.

pneumonia)

Ornithosis (pigeon, chicken, etc.

pneumonia)

Ailourosis(?) (cat pneumonia)11

Lymphocytic choriomeningitis

"Mongoose" virus(?)

"Cotton rat" virus(?)

Feline pneumonia virus¹⁵

Ill-defined^{8,9} and unknown varieries

Epidemic, Winter Month Forms

Influenza A

Influenza B

Measles

"Cotton rat" virus(?)

Unknown varieties (colds, grip,

etc.)

dence suggests that bacteria sensitive to sulfonamide compounds have become secondary invaders, or if an epidemic of pneumococcal pneumonia is extant, or if pneumococci of the lower numbered types are present in the nasopharynx, chemotherapy is justified, but it should be discontinued if, in a reasonable period, the disease fails to respond.

Convalescent serum from patients who have recently recovered from a viral pneumonia has also been used in therapy and a few clinicians claim to have observed beneficial effects. In view of the diverse causes of the syndrome, this method of treatment seems to be empirical to say the least. Even specific convalescent serum once thought to be helpful in psittacosis, has long since been given up as useless.

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THE NATURE OF PSYCHOTHERAPY*

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P SYCHOTHERAPY is as old as medicine: indeed, it is nearly as old as religion; and a history of psychotherapy would be a history of human culture. Yet it is only the last half century that has brought scientific knowledge of its scope and limitations; and it is only in the last half century that anything new has been added to its techniques.

In the perspective of history, the term itself is young. Yet it has already acquired a meaning so vague and general as to be difficult to use with precision. It can include the mystical healing rites of a priest-physician of ancient Greece, or the drum-beating and the voodoo practices of a modern primitive, David strumming his lyre against Saul's melancholy or classes in rhythmic dancing in a modern psychiatric clinic, forced labor in an old prison asylum or the rhythm of a modern occupational class in basket weaving. As one witty patient described it, "under one, and over two, rest in a neutral environment."

In this loose sense, psychotherapy embraces any effort to influence human thought or feeling or conduct, by precept or by example, by wit or humor, by exhortation or appeals to reason, by distraction or diversion, by rewards or punishments, by charity or social service, by education. or by the contagion of another's spirit. This broadest possible use of the term would also include the temporary lift of spirit through music, art, or literature.

Such methods as these depend upon an artful blend of imagination, feeling, intuition, firmness and common sense; but it will be our thesis that as a science psychotherapy begins only where these leave off. It happens that it usually will be good common sense to give water to a thirsty man; but this is not science until we know the role of water both in the normal body and in its pathology. So too with all such simple psychotherapeutic sips of water as sympathy or advice or rewards and punishments: we use these with scientific precision only when we

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know their relationship to normal and disturbed functions of the mind. Therefore, our first task is to formulate a concept of psychological normality and to define the boundary line between normality and neurosis.

We will not be aided in this by any distinction between normal and neurotic which is based on the usual differential points. We are not concerned with the issue of whether a man knows the difference between right and wrong in the archaic and unrealistic legal sense, nor with the question of whether he believes that he knows what he is doing and why he is doing it, that is, whether he can rationalize his conduct. Nor are we concerned whether his conduct conforms to the social and cultural mores of any special time and place, or whether it is extravagant and fantastic or orderly and sedate. These are important aspects of behavior but not basic or constant in their implications. Thus it is normal to wash one's hands but not normal to have a handwashing compulsion, although there is nothing eccentric or anti-social or deviant from any culture in the mere act of handwashing. Similarly, to stand on your head in a tumbling act is normal, while to stand on your head in church is not; unless perhaps it is done to pay an election bet, or as a hazing stunt. Evidently the critical difference must be sought neither in the act nor in its setting, but in the determining mechanisms of the act. Behavior is normal or abnormal because of the nature of the inner forces which produce it.

What then are the characteristics of the inner determining forces which make any moment of thought, feeling, and action normal, and what are the characteristics which make it neurotic. The answer to this requires one further distinction—a distinction between forces which are within the range of our conscious perceptions, and those which are so deeply buried as to be inaccessible to any introspective knowledge of ourselves. It is as difficult for men who are unfamiliar with this field of phenomena to realize that unconscious yet psychologically powerful forces are constantly at work in everyone, as it was for the old scientist who had never looked through a microscope to believe in the microscopic objects which von Loevenhoeck described. Nevertheless it is one of the great achievements of modern science that the evidence for this has become incontrovertible. It is not possible to describe this evidence in detail; but it is important to note in passing that it is firmly based on a variety of different techniques applied to four fields of observation: to wit, experimental work with humans, clinical observations with psychoanalytic methods, clinical observation of animal behavior, and experimental work with the conditioned reflex. The weight of this varied evidence forces the psychiatrist to proceed from the premise that in every moment of human life the mosaic of thought, feeling and conduct which constitutes behavior is determined by confluent forces, that we can be aware of only a fraction of these forces at any time, and that we tend naively to overestimate the relative power of those of which we are aware even in events in which the unrecognized forces have played a determining role. To simplify our terminology, we can use a somewhat inaccurate foreshortened jargon and say that while we are conscious at any moment of some of the reasons for our conduct we are always unconscious of others.

But how does this help us understand the distinction between the normal and abnormal in behavior? Here we are on clear grounds. Whether "conscious" or "unconscious" forces play a major part in producing any moment of behavior is the most important single distinction in human psychology. This is because conscious motives are constantly. molded by external realities, whereas unconscious forces pay no heed to the outside world. They are uninfluenced equally by the pain that they may cause the individual himself and by the pain which they may inflict on others. They are deaf to exhortation, argument, and reason, or to appeals to love or hate. They are so blind that the symptomatic acts which they engender do not succeed in satisfying even themselves. Their tensions remain undischarged. Therefore they are literally insatiable. Consequently, the larger is their influence in any particular act, the more unrealistic do they make that act, and the more inflexible and the more endlessly repetitive it becomes. This is what has been called the "Repetitive Core of Neurosis," Kubie: 1 and this is why neurotic behavior is endlessly and ceaselessly repetitive, whether it appears in the form of overt neurotic symptoms or of neurotic life patterns disguised as ordinary behavior. This is what the layman means when he says that we learn so little by experience. It would be more accurate to say that the consciously organized normal aspects of man can learn by experience, but not that part of him which is unconsciously driven: because the unconscious neurotic mechanisms go on their way unsated by gratification and unaltered by experience.

It is precisely this repetitiveness which constitutes the essential challenge to psychotherapy and its most difficult problem. However, the

approach to this ultimate stronghold is always preceded by less complicated preparatory maneuvers. These simpler psychotherapeutic expedients may be grouped under three main headings: (a) Practical support—consisting primarily of advice, guidance, and assistance in the management of life situations and environmental difficulties through social service aids, etc. (b) Emotional support—consisting essentially of sympathy, exhortation, admonition, encouragement, humor, art, recreation, companionship, etc. (c) Reorienting education—consisting primarily of efforts to alter the patient's habitual attitudes of guilt, fear, hate, and depression, by educating him to tolerate his own conscious and unconscious needs and cravings, his instinctual hungers, his familial jealousies and hates, etc.

The third of these groups requires extensive knowledge of unconscious psychological forces, and hides many subtle dangers which will be discussed below. The first two, however, can hardly be called a discovery of the psychiatrist. They are the homely non-specific, commonsense weapons of every wise parent and teacher. They must always be tried first. Indeed where they succeed alone, one may be sure that the maladjustment is more external than internal: since it is precisely their failure which reveals the rigid repetitiveness of behavior which is energized predominantly by unconscious internal forces, rather than by external environmental stresses. This again is why we say that psychotherapy as a science begins where the simple, rational methods fail.

Perhaps a banal example can make this clear. A child of three or four wakens at night, slips out of his bed, and comes pattering into the front room in search of his parents. On the first occasion he is picked up, hugged, and carried back to his room; and after his wants are attended to he is tucked in, kissed and left there. A few minutes later, however, he reappears. The same "medicine" is applied, perhaps a little more brusquely, but nonetheless kindly. Even if it didn't work the first time it might work now. But again the youngster appears. The parents try successively leaving the light on or the door open, a toy in his bed, cuddling, promises, bribes, scoldings, threats or punishments; but in spite of their versatile efforts the child appears over and over through the course of many evenings. This is a typical transient neurotic episode of childhood. The parents become distracted. They run through the whole gamut of human feelings, from affectionate patience to irritability, anger, and finally a panicky feeling that something is wrong.

They feel that they have tried every possible sensible device, without success. They do not realize that their failure constitutes a thorough therapeutic test, demonstrating that the roots of the child's disturbed behavior lie deeply buried, on a level which is inaccessible to any surface manipulations.

What is true of the small child is also true of the adult. Rewards and punishments, discipline and education, argument and reason, the sensible manipulation of the environment, occupational therapy, comfort, solace and exhortation, these are all essential preliminary steps in the approach to any psychotherapeutic problem. They clear away external complications. They effect cures when the situation is sick rather than the individual. Thus they are at once the ante-chamber to deeper treatment, and a therapeutic test of its necessity. Where they work it is folly to go deeper: but where they fail it is even greater folly to persist with education, habit training, social service, work adjustment, etc., because, until he is already on the road to health, the neurotic patient cannot use such aids, no matter how badly he needs and craves them. For the neurotic, treatment must precede practical assistance: or the wisest guidance will be sabotaged by the neurosis.

But psychotherapy cannot always achieve or even aim at the eradication of causes. As in any other medical discipline, it must sometimes content itself with palliative measures.

Palliative psychotherapy consists primarily of an effort to teach patients how to live with some measure of comfort within the confines of their uncured neuroses. Of itself this can relieve much suffering. For instance, an agoraphobia may manifest itself first merely in an uneasy feeling in very large, open spaces. At this stage the neurosis will make little difference in a patient's life. Gradually, however, the anxiety will become more all-pervading, until the patient becomes unable to go out of doors at all, or even to go into a moderately large room. With each successive encroachment on his freedom, his life and that of his family become more circumscribed. Soon all who know him begin to pay with him the price of his neurosis. If the psychotherapist does no more than to keep the patient from succumbing to these successive restrictions, he will contribute greatly to the happiness of the patient and of his family. It is here that education, exhortation and endless ingenious manipulations of the environment can play a role of major importance.

If more than palliative treatment is to be attempted, the psychothera-

pist must attack the rigid, inflexible, automatic, repetitive core of the neurotic process. It will be seen that this challenge cannot be effectively met in the naive spirit which underlies the time-worn concept of "habit training."

It is not orthodox to place this rigid repetitive tendency at the very heart of our psychotherapeutic problem: yet I do so because I believe that this is the nucleus which is common to all neurotic processes, and that the customary emphasis on mood and content is an emphasis on secondary symptomatic manifestations. When the repetitive process manifests itself in certain recurrent ideas we speak of obsessions, in recurrent acts we speak of compulsions, in recurrent mood states we speak of anxieties, depressions, elations, etc., and in recurrent distortions in the patient's view of external reality we speak of delusions. These variegated secondary symptoms demand flexible temporizing care: but they are the branches and not the roots of the tree. It is towards the roots, i.e., the forces that make the disturbance recur, that our therapeutic efforts must be directed.

First, however, we must raise one more important preliminary question, namely, whether the repetitive pattern ever becomes so structuralized in the nervous and glandular organization of the individual as to be unalterable by experience on the psychological level; or whether the mechanism by which that force is mediated can be altered by means of psychological events. On the answer to this question hinges the future of all psychotherapy: yet the answer is not known. We know that the duration of a symptom is no indication as to its structuralization. For instance, as a result of purely psychological treatment I have seen a man of 57 lose symptoms which began when he was three years and ten months old: while in other cases, in spite of penetrating insight into buried forces, quite recent symptomatic manifestations may persist almost unaltered. We do not yet know why this is true. It is possible that in certain patients the nuclear repetitive phenomena may be the expression of an inherent organic inclination towards such repetitions. We know that repetitive phenomena occur universally and from infancy onward; but as yet no quantitative studies are possible of their incidence, of the factors which produce them, or of their correlation with later neurotic manifestations. In brain injuries and in certain experimental lesions repetitive phenomena may be produced; and Brickner² has shown that the stimulation of a certain area in the brain can induce persevera-

tion. This does no more than suggest the possibility that organic factors may play a role. It gives no information as to possible variations in the inherent inclinations of different brains towards the production of repetitive states under similar psychological stresses. Therefore, we are left with several alternative possibilities, which are not mutually exclusive. In the first place, there may be a greater inherent inclination towards stereotyped repetitive phenomena in one brain than in another. Secondly, certain types of gross or subtle injury to the brain may possibly enhance this tendency. Thirdly, psychological influences of varying severity can induce this phenomenon. Presumably if sufficiently intense they can induce the phenomenon in any central nervous system: but it is also possible, if not probable, that in certain nervous systems they can be induced more readily than in others, and that once they arise in certain brains they may thereafter be more tenacious than in others. Finally, repetitive phenomena once induced may be mediated by reversible changes in one nervous system, and by irreversible or even progressive changes in another. It is particularly in such cases as this that lobotomy may be a rational procedure. Our knowledge of all of these matters waits upon the development of methods by which these hypothetical variables can be measured. In the absence of such methods in our pursuit of therapeutic weapons we are forced to rely upon the oldest device in medicine, the method of trial and error. Let us turn to the errors first, to dispose of them.

Throughout his life every psychiatrist learns one lesson over and over again, only to forget it, namely, that however much it may relieve his own feelings it does no good to a patient to call his illness names. When a patient comes with a frank symptom, such as a 'hand-washing compulsion, we know that it is a mere waste of breath to tell him solemnly that he suffers from a compulsion. The patient tells us that himself. Our technical nomenclature can help him neither to control his symptom nor to get rid of it. Nevertheless, when dealing with subtler compulsive patterns this is forgotten, and psychiatrists hopefully describe to patients their "neurotic trends." There is no parent who in layman's terms has not told his child the same thing, calling him lazy or good-for-nothing or disobedient. Scientific name-calling is not more effective than this: because scientific epithets can not alter the repetitive nucleus of a single neurotic manifestation. At worst they merely mobilize the patient's defenses. Jung and Adler and Rank all made that mis-

take. It is regrettable to see it recurrently repeated by others. Many years ago William Allen White pleaded against this error, when he said that the hardest lesson a psychiatrist has to learn is to allow a patient to say that 2 plus 2 equals 5, until the patient discovers why he *bad* to cling to this belief.

It is impossible to lay too much emphasis on the futility and dangers of naive confrontation; because this is the most frequent mistake of the immature psychiatrist, and of the well-intentioned general practitioner who has read psychiatric theory without having rigorous drill in its procedures. Superficial confrontations which merely describe the patient to himself without long and patient preparation, inevitably precipitate resentment and mobilize his defenses. Premature confrontations which reach to deeper levels, challenging the patient to recognize some of his deeper fears, yearnings and hates, must either be rejected as far-fetched or else they will precipitate the patient into unmanageable terror, guilt or depression. One learns slowly never to force a patient to look at a painful fact about himself until you are in a position to explain its origin in his history and its function in his present life. This may take patient exploration over many months.

So important is this that we must recognize that it may be dangerous to attempt to argue a patient out of cherished ideas and beliefs even about seemingly impersonal affairs, such as science or politics. Argument may be as dangerous as confrontation. If it succeeds in breaking down the defensive barrier of symptomatic ideas, all that can be achieved is a sudden eruption of overpowering emotions.

Thirdly, there may be danger even in reassurance or consolation. A patient said a few mornings ago, "I was in a panic. My sister telephoned me and assured me that her household were well. Then all of a sudden I found myself in such a depression that I stood at the window and thought of throwing myself out." It is not too much to say that the only safe thing to do with a patient is to listen to him, until one understands enough about him to be in a position to relate everything one says and does to his unconscious psychological processes.

And now we are ready at last to suggest a possible answer to the final question: namely, what is the nature of a psychological process that can influence the basic underlying repetitive patterns which characterize all neurotic phenomena? This may not be too difficult to understand if we recall that the repetitive pattern is a recurring effort to bring to a

satisfactory completion a painful, forgotten, and incomplete experience which has been left hanging in air. Thus the child who wakens in the midst of a nightmare puts himself to sleep again by telling himself a happy ending. The man who has been worsted in an altercation goes down the street muttering all the fine things that he might have said had he only thought of them in time. Indeed we do this throughout life, the only difference being that most of our attempts to discharge the tensions left by past experiences are carried through without our knowing what we are doing.

In such experiences, moreover, the boundary line between reality and dream is never hard and fast, because each "experience" is a mosaic of fact, confusion, misunderstanding, and fantasy. The past which we try vainly to undo is half real and half imaginary: but the neurotic shadows which it casts on the present screen of life are real enough. The neurotic component in all of us is always the residue of just such incomplete experiences, nightmares which have not lost their emotional hold even after we have wakened, nor after we have forgotten the dreams themselves. It is as though we had wakened just as the villain was poised to strike. Then we "forget" the dream but not the feeling, and live out our waking lives through symptoms or symptomatic acts which are disguised and unsuccessful attempts to avert or avenge the fancied blow.

One characteristic form of the acute traumatic war neurosis gives us a clear picture of this process. Night afer night the patient attempts self-cure. That is, he redreams his shattering experience, trying each time to dream it through to a happy ending. But as he dreams, his terror mounts to a point at which he is wakened prematurely at the very climax of danger. This leaves him shaken with terror, grief and rage. There is a point in the dream beyond which he cannot go, some mingling of reality and fantasy so highly charged that every time he tries to re-live it his mind shies away at the last moment like a horse that refuses just before the take-off. Just as this happens spontaneously in the war neurosis, so it occurs in the treatment of the neurotic patient. He, too, must shy away from deeply painful if less melodramatic early experiences, whenever the therapist tries to help him re-live them to a realistic conclusion, thus to free him from the endless, closed repetitive circles of his neurotic patterns.

This incessant struggle is the source of a state of constant inner tension, for which the most obvious therapy would be a discharge of the

pent-up feelings. The process of discharge is often called "catharsis," and much is made of it in psychiatric literature. Therefore, it is important to know that catharsis is not enough. Furthermore, the concept is poorly understood and widely misused. Any discharge of emotional tension can give temporary relief, be it a temper tantrum or an uncontrolled outburst of crying and laughing. Even a painful symptom gives momentary relief. The patient with a compulsion neurosis discharges tension in the moment in which he executes his compulsion. In fact, every act and thought and feeling discharges tension in some measure; and all of this is catharsis. Unfortunately, however, most of these acts rapidly recreate as much tension as they discharge, and sometimes more. In a somewhat more lasting sense, however, it is cathartic to help a patient to express pent-up feelings which he has previously been afraid or ashamed to face. A man who has never been ready to admit that he hated some member of his own family may find marked relief when the psychiatrist's non-critical attitude encourages him to acknowledge this feeling. But even here, a fresh up-welling of guilt or anxiety can exact a heavy price for the catharsis, and precipitate the patient into graver depression and terror. Thus, no mere discharge of feeling, either from the surface or from the depths, can accomplish lasting benefits unless it is preceded and accompanied by an eradication of the source of the feelings. Without this, the feelings inevitably recur.

A psychotherapy which aims at the eradication of etiological sources must recover the content of the forgotten dreamlike "experiences," since it is these which give rise to the feelings which produce symptoms. They are the links in the chain of conditioning experiences. Therapy must complete the dream, in order to dispel the haunting moods which flow from it. It must find the happy ending which the child in us seeks incessantly. And in order to recover that which was forgotten it must penetrate the mists which shroud the past, and enable the patient to relive vividly the acutely painful and confused experiences which make up the "dream."

All of the defensive forces of the patient's personality are mobilized against any such effort to penetrate into the forgotten areas of experience, because they have been "forgotten" not by accident, but as an obligatory defense against the pain of the original experience. Therefore, every technical advance in psychotherapy has been in the direction of finding ways around these defensive barriers.

This whole matter is widely misunderstood. The question is asked, "Does the rediscovery of past events automatically dissipate feelings which had their roots in those particular events?" Or in another form the question is asked, "Does the discovery of a secret purpose, yearning, or desire automatically dissipate that purpose?" In reality these are not two questions but one. It is not merely the recovery of an event which releases the patient, nor merely the recovery of the event plus the feelings and desires which derive from that event. It is the discovery of the totality of the purposes, the hopes, the fears, the loves, and the hates which animated the individual at the moment of the event, plus what that event did to those purposes, loves and fears and hates, and how these were deviated by that event from their initial pathway onto another. This, and not less than this, is the potent discovery. If at a certain moment in the life of an individual the bank of a river assumed a terror-laden significance and if that moment and all of its attendant circumstances were subsequently "forgotten," then the terror becomes isolated, like a station with no railroad tracks leading to or from it. The terror can be experienced but only about substitutes; and can never be discharged. And the recovery of the memory of the moment when for the first time the bank of the river acquired a nightmarish quality allows the whole structure to be dissipated, until the bank of the river again becomes only a bank of a river and nothing more. The recovery of facts thus is merely a necessary part of the total process of undoing experience, of deconditioning the human animal. This is why "habit training" is a naive and empty concept.

All highly charged symptoms acquire many meanings through the course of life. Consequently, in retrospect one must trace its evolution through a series of discoveries, each of which gives temporary relief and then a disappointing recurrence of pain. This has led some theorists to the easy conclusion that the discovery of the genetic experiences is unimportant. This is equivalent to saying that it is unimportant to discover the bacterial organism which causes an infection if you cannot always prepare a powerful antitoxin from it.

A full consideration of the methods of recovering the past would involve us in difficult technical details concerning the handling of various types of resistances and transference phenomena. It is not possible to do justice to these problems here; but it may be useful to emphasize that the strength and power of the patient's defenses constitute the final

reason why blunt confrontation is worse than useless, usually serving merely to increase the patient's opposition, and throw him into panic, and from panic into rage. In turn, this is why all short-cuts are dangerous.

During recent years various methods have been developed by which this goal is pursued. The most important of these is psychoanalysis; not because it is a perfect instrument, but because it is still the pathfinder. Hypnotism, which once was used naively as a magic wand with which to order symptoms to disappear, has more recently been used as a method to assist in the recovery and re-living of the past. It is used both in combination with and as an extension of psychoanalytic technique. In turn, both of these have been used in combination with medications of various kinds; and experiments are under way in their use in combination with hypnagogic states. Finally, even the various forms of shock treatment come into consideration in this connection, because they sometimes render material accessible which is otherwise hidden behind the repetitive patterns of thought and behavior. Shock treatment can be used, therefore, not merely as a crude way of disrupting temporarily the associative pathways, but also to render accessible to investigation the life experiences which lie buried behind those patterns.

Not one of these methods has as yet established beyond argument its own territory of assured pre-eminence, nor its own limitations. Each is in the developing, testing and formative stage. Few psychiatrists would agree to any formulation of the indications or contraindications of any one of them. Under these circumstances, little would be gained by putting forward my own views of the moment: especially since they, too, will undoubtedly change with the experiences of tomorrow. However, if we have succeeded in making clear the basic principle and goal which underly all of them, and if we have brought the concept of psychotherapy into harmony with scientific medical attitudes on the relationship of therapy to etiology, then I will feel that the main purpose of this paper has been achieved.

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THE DIAGNOSIS OF CANCER OF THE PROSTATE INCLUDING THE INTERPRETATION OF SERUM PHOSPHATASE VALUES*

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If the philosophy of diagnosis, two medical aphorisms must be openly or tacitly assumed, both of which apply to prostatic cancer. R. C. Cabot frequently stated the first; that the symptoms of any disease may be none. The second consideration follows: in order to make a diagnosis one first must have the disease in mind. The clinical picture of some diseases is so apparent as to compel recognition, as in complete urinary retention from prostatic cancer; or the manifestations of disease may be highly subtle and obscure, as when metastasis of a prostatic tumor produces chest pain or sciatica, the primary lesion being asymptomatic.

The diagnosis of prostatic cancer is frequently satisfactory since chemical methods exist by which the disease often may be recognized in the laboratory. The final aim of diagnosis is to recognize disease by chemical methods without seeing the patient. Laboratory determination of "What Label" and its yardstick "How Much" is of first importance in classification, in evaluating therapy and even in initiating new forms of treatment. In prostatic cancer, laboratory testing of blood from the veins of the antecubital fossa is of significance.

Cancer of the prostate is the cause of death of about 5 per cent of men over fifty years. The diagnosis of clinically active prostatic cancer often is easy since usually the lesion is far advanced and has metastasized when the patient presents himself for treatment. Clinically active prostatic cancer, in any early stage suitable for total excision of the entire gland, usually can be recognized provided palpation of the prostate per rectum is carried out; such early lesions, however, are not often detected at present. An interesting observation of the pathologists is the frequent presence of occult, miniature prostatic cancers which do not cause mor-

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|---------------------------------------|----------|
| SYMPTOMS OF PROSTATIC CANCER 50 CASES | |
| INCREASED URINARY FREQUENC | |
| DECREASED URINARY STREAM | 7.8% |
| ACUTE URINARY RETENTION | 28% |
| DECREASED WEIGHT | 58% |
| SCIATICA | 36% |
| LUMBAR BACK PAIN | 40% |
| OTHER BONE PAINS | 14% |
| PERINEAL PAIN | 12% |
| NARCOTIC ADDICTION | a |
| HEMATURIA | 8 |
| PARAPLEGIA | 4 |
| EDEMA OF LEG | 4 |
| | · |

TABLE I

bidity; the incidence of these lesions in the prostate gland of men over 50 years of age examined routinely at autopsy, ranged from 14 per cent (Rich), 16.7 per cent (Moore) to 46 per cent (Baron and Angrist¹). It is clear that the diagnosis of these small silent lesions cannot be made except by guess on a statistical basis, and indeed it is perhaps of little clinical importance; however, in view of the stimulating effect of male sex hormones on prostatic cancer, it is well to bear in mind that these small occult lesions exist with frequency in older men, when these hormones are administered to men over fifty years of age.

Symptoms of Prostatic Cancer: A typical history for a run of the mine case of prostatic cancer is that of a man over fifty years of age who has increased frequency and some difficulty on urination, with pain in the lower back and loss of weight.

The usual symptoms of prostatic cancer depend on interference with micturition by the primary tumor, or by osseous or lymphatic metastasis; or as a result of the cachexia of carcinomatosis. It is uncommon for the metastases of prostatic cancer to produce important symptoms except through involvement of bones or the regional lymph nodes. Nearly all patients have increased urinary frequency and difficulty in voiding (Table 1); hematuria usually is not present. In our experience 56 per cent of the cases suffered from pains in the bones, the result of metastasis. Most commonly these symptoms are in the lumbar region or legs; they may arise in any other part of the spine with radicular radiation.

The age incidence of prostatic cancer is of interest; the disease is essentially that of men over fifty years, and we have seen only one case in a person (aged forty-seven years) younger than this age.

Physical Findings in Prostatic Cancer: The characteristic findings are obtained on rectal examination and consist of a stony hard, nodular, craggy involvement anywhere in the prostate. In early disease, the nodule is single; in later disease multiple nodules with infiltration along the seminal vehicles are present. It is very rare for prostatic cancer to ulcerate into the rectum; most of the ulcerative neoplasms on the anterior rectal wall in the prostatic region are rectal tumors.

Single hard nodules, not caused by carcinoma, have been encountered occasionally in our experience, and have been due to prostatic calculi, tuberculosis, non-specific infection, as well as benign prostatic hypertrophy, which is usually the most puzzling condition to be considered in differential diagnosis. Roentgenologic examination of the pelvis should always be made in suspected or definite prostatic malignancy and will demonstrate prostatic calculi if they are the cause of nodule formation.

Roentgenologic Findings in Prostatic Cancer: In a series of fifty patients with advanced prostatic cancer, x-ray evidence of osseous metastasis was present in thirty-one cases. Both osteoblastic and osteolytic types are found; usually they occur together. Only in two cases were osteolytic lesions alone encountered; these lytic lesions are commonly small and multiple compared with the large "melting away" that is often seen in hypernephroma. The pelvis was always involved when metastases had occurred in the bones, and lesions were never encountered distal to the knee or elbow joints. Other bones are often involved, but as a routine measure of search for metastases, raying of the pelvis alone is regarded as an adequate device. In the improvement which occurs following endocrine treatment, osteolytic lesions become sclerotic.

The chief confusing entity in x-ray diagnosis of prostatic metastases to bone occurs with Paget's disease (osteitis deformans). The fundamental x-ray evidence of Paget's disease is an increased grossness of trabeculae with cyst formation; the trabeculae become massive. In prostatic cancer the trabeculae of bone disappear, incorporated in dense osteosclerotic masses.

Pathologic Diagnosis of Prostatic Cancer: It is occasionally necessary to resort to biopsy to make the diagnosis of cancer of the prostate. Several methods of approach are available and each of these has definite

indications. The perineal approach with removal of a section of the gland, is best done in suspected early cases, where radical prostatectomy can be carried out immediately if the diagnosis is confirmed. If there is prostatic obstruction in advanced cancer, transurethral resection of the prostate should be carried out since in addition to obtaining tissue for biopsy the obstruction may be removed effectively. The author has had no experience with the valuable method of aspiration biopsy which has been developed at Memorial Hospital.

The essential criteria for pathologic diagnosis are anaplasia and invasion. The relation of the small acini to the surrounding stroma in adenocarcinoma is of importance.

In differentiating carcinoma primary in the prostate from bladder carcinoma or other malignant disease in this neighborhood, valuable aid is often obtained by staining the tissue for acid phosphatase by the technique of Gomori, since prostatic epithelium contains much larger amounts of this enzyme than other tissues. The tissue requires special fixation in acetone preliminary to staining for the sites of enzymatic action.

Cystoscopic Diagnosis of Prostatic Cancer: When prostatic cancer is associated with benign prostatic hypertrophy, as not infrequently occurs, only the benign lesion is visible at cystoscopic examination. Unaccompanied by hypertrophy, advanced prostatic cancer often displays suggestive features; such as constriction of the posterior urethra and infiltration of the trigone. A common sign is the appearance of small irregular notches around the vesical neck compared with the notches found in prostatic hypertrophy which resemble formal architectural figures, Gothic in type.

Serologic Diagnosis of Prostatic Cancer: This important diagnostic procedure was developed by A. B. and E. B. Gutman^{2,3} of Columbia University and Barringer and Woodward⁴ of Memorial Hospital independently in 1938 and depends on the important discovery of Gutman, Sproul and Gutman (1936)⁵ that prostatic cancer contains large amounts of acid phosphatase. In brief, there exist two distinct enzymes, acid and alkaline phosphatase, which are capable of splitting monophosphoric esters to form inorganic P.. Alkaline phosphatase is particularly rich in concentration in the osteoblasts and when there is brisk osteoblastic activity the value of this enzyme is increased in the blood serum; such states include rapid growth in children, Paget's disease, osteogenic sar-

coma, osteoblastic metastasis from prostatic cancer, etc. This enzyme is also increased in liver disease where it is an exquisite indicator of hepatic function. So far as is known, bone activity and hepatopathy are the only conditions in which the serum values are increased.

Acid phosphatase values of serum are significantly elevated only in cancer of the prostate and in this condition only when metastasis has occurred. In the author's laboratory^{6,7,8} the King and Armstrong method, with appropriate buffering, is used for determination of both enzymes; the normal values are, for acid phosphatase, less than 4.5 units; and for alkaline phosphatase, less than 12.5 units, each per 100 cc. of serum. In a series of 100 cases of advanced prostatic cancer before treatment, one or both of the phosphatases were increased in 52 per cent, and both were in the normal range in 48 per cent; with osteolytic metastasis alone the phosphatases were never increased. Usually when there is an elevation of phosphatases, both are increased; however, in one case only the acid value was high and in five cases only alkaline phosphatase was elevated. When the serum acid phosphatase is significantly raised (greater than 10 units) it is certain that the patient has prostatic cancer with metastasis; values between 5 and 10 units are presumptive of prostatic cancer, but are occasionally observed in other conditions. Patients frequently have advanced prostatic cancer even with metastasis to the bones accompanied with serum phosphatases in the normal range, but if both phosphatases are distinctly increased the diagnosis is established that cancer of the prostate with osteosclerotic osseous metastasis is present; there are false negatives, but no false positives. These tests are of special value when roentgenograms of the bones show equivocal changes. It is obviously necessary to determine both of the phosphatases for maximum efficiency in diagnosis and prognosis of cancer of the prostate; these tests are as clearly necessary as studies of basal metabolism in thyroid disease.

Prognostic Implications of the Serum Phosphatases in Prostatic Cancer: I believe that it has now been established that the prostatic cancer cells flourish in the presence of physiologically effective amounts of male sex hormones, and often retrogress, more or less, when the testicular androgens are eliminated through bilateral orchiectomy or are neutralized through estrogen administration. The course of the disease may be followed well by frequent serial phosphatase determinations. Characteristically when subjected to hormonal modifications in those patients with

phosphatase elevation, the acid phosphatase level rapidly falls after initiating treatment, while the alkaline phosphatase values rise for some weeks (a favorable sign) and then fall to or towards normal. In some patients the values having reached normal have remained so for at least 800 days following orchiectomy.

In one patient with complete paraplegia resulting from metastatic cancer of the prostate, the alkaline phosphatases precipitously fell to normal in the few weeks in which the paralysis was disappearing following orchiectomy; this fall, not preceded by the characteristic rise was attributed to the bony atrophy of disuse accompanying the high paraplegia. When the phosphatases do not return to normal, following endocrine modification, the prognosis is unfavorable. In a group of patients in whom the clinical and chemical response to this treatment is favorable, after some months alkaline phosphatase values again climb accompanied by clinical evidence of activation of the disease: this enzymatic response is likewise unfavorable.

Certainly, frequent serial phosphatase determinations in prostatic cancer have passed from the stage of being merely an important laboratory tool to an essential clinical status in the diagnosis and prognosis of cancer of the prostate.

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THE MANAGEMENT OF THE ACUTE EPISODE IN CORONARY OCCLUSION*

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the death rate from heart diseases has more than doubled during the last 40 years. Deaths from heart diseases in 1940 totaled 385,191, a rate of 292.5 per 100,000 population. This was the greatest number of deaths ever recorded from heart diseases.

Although there have been appreciable decreases in heart disease death rates in the low age brackets, the rate of heart disease fatalities has increased considerably in the upper age groups; for example, 45 to 54 years from 173.01 to 279.5; 55 to 64 years from 414.1 to 713.5; from 65 to 74 years from 957.3 to 1,723.5. Most of the deaths in these groups were due to coronary artery disease or its complications including coronary occlusion and myocardial infarction. This gives some idea of the prevalence of the condition, treatment of which I have been assigned to discuss this afternoon.

Definition of terms: The title of this discussion would probably be more correct if myocardial infarction were used in place of coronary occlusion. Recently some confusion has arisen concerning the terminology in coronary artery disease, due probably to several new expressions suggested such as coronary occlusion, coronary failure and coronary insufficiency. The term acute myocardial infarction seems to fulfill the requirements since the clinical signs and symptoms are all on the basis of myocardial necrosis. Then too, it is known that this lesion may occur without coronary thrombosis or without acute coronary occlusion, and contrariwise, occlusion or thrombosis of a coronary artery may occur without producing a myocardial infarct. As the studies of Blumgart and Schlesinger indicate, there is no characteristic clinical syndrome associated with coronary artery occlusion per se. The symptoma-

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tology is usually the result of an infarct.

Arbitrarily the first three weeks were chosen as the phase of myocardial infarction to be considered in this talk. An analysis of some 200 cases of myocardial infarction² on the Third (New York University) Medical Division of Bellevue Hospital demonstrated that most of the complications and sudden deaths occur during the three weeks after the onset of the illness. It is obvious, therefore, that this is the critical period of the disease.

Diagnosis: In the typical case of myocardial infarction the diagnosis is easy, in fact, is often apparent from the history alone. Although the problem of diagnosis will not be discussed, I should like to stress the importance of early recognition and the institution of immediate treatment since they have a decided influence on mortality as well as future expectancy of life. As already mentioned the early phase of this disease is usually the critical period. In a patient in whom a diagnosis is not obvious bedrest should be maintained until the correct diagnosis is decided upon and thereby give the patient the benefit of the doubt. The subsequent appearance of additional clinical manifestations indicative of infarction and the alterations in repeated electrocardiograms will usually establish the true nature of the disease even in the bizarre or atypical cases.

Preatment: Thrombosis which is the precipitating factor in some 60 per cent of cases with myocardial infarction is not instantaneous and may extend over a period of hours, days or weeks. Premonitory symptoms in such instances may precede the acute episode of infarction over the same period of time. It has been suggested that heparin, and more recently dicoumarin³ (dicumarol), the new anticoagulant, might be useful in such cases in preventing complete obstruction and, in turn, infarction. Experimentally the basis for this rests in the work of Best and his collaborators^{4,5} in dogs in whom heparin prevented the thrombosis which usually occurs in their coronary arteries after sodium ricinoleate has been injected into these vessels. This suggested the possibility of its use clinically in the initial stages of coronary thrombosis; or, if thrombosis be already complete, heparin might arrest its extension, or prevent mural thrombosis which not infrequently occurs in the ventricles over the site of the infarct and which acts as a source of emboli.

I have failed to find any reference in the literature relating to such use of heparin. Best⁵ states that "it has been used in a few cases of coron-

ary thrombosis in human beings but not as yet in a scientific manner." Several isolated cases apparently have been known to have been reported at various meetings but these have not as yet been published.

As to dicoumarin (dicumarol) the new anticoagulant agent isolated from spoiled sweet clover, I have just been informed that it has been employed recently in four cases of coronary thrombosis, one under the supervision of Duryee⁶ at the New York Post-Graduate Hospital and the other three at Welfare Hospital under Prandoni.⁶ In all four instances it was administered in doses of 100 mgm. per day by mouth over periods ranging from twenty-one to twenty-eight days. All four patients had uneventful courses and recovered.

It is Best's⁷ feeling, and I agree heartily with him, that the results in a few cases in which any anticoagulants have been employed are not significant, and that until a series of such cases with adequate controls have been made available, it is rather useless to discuss the results of the use of anticoagulants in the treatment of clinical coronary disease.

As soon as the diagnosis has been established every effort should be made to obtain complete physical and mental rest for the patient. He should be put to bed immediately, preferably in a Gatch bed, and not moved from it for at least a month. If transportation is necessary it should be by means of an ambulance and, if possible, postponed until at least the end of the third week. Under no circumstances should he be moved to a hospital merely to obtain special records such as electrocardiograms or other laboratory data.

The mainstay in the management of this disease is the reduction to a minimum of the demands on the heart and circulation. To this end the patient should be kept in bed and not be permitted to move about unnecessarily. During the first week or so he should not feed himself. Examinations of the patient, with the exception of auscultation of the anterior chest, should be infrequent during the first few days.

Special nursing care should be instituted immediately. Day and night nurses are essential with special attention to the ability of the night nurse who should be alert and conscientious during her stay on duty. Careful nursing is one of the most important factors in the successful recovery of the patient. No visitors except those in the immediate family should be allowed in the sick-room during the first week. All visits should be curtailed to only a few minutes.

Complete mental relaxation bordering on drowsiness should be maintained during the first few days or even the first week. Highly exciteable, apprehensive or temperamental patients are much better off if kept asleep more or less continuously during the early phase of the illness. Some form of a sedative or an opiate may be required to accomplish this. In the absence of pain one of the barbituric acid preparations such as phenobarbital in doses of 30 mgm. (½ gr.) or amytal 0.1 gm. (1½ gr.) given three times a day may be sufficient to keep the patient at ease, drowsy or even asleep. Chloral hydrate or sodium bromide or both may also be given several times daily with good results.

Before leaving this part of the treatment, let me remind you that alcohol is of distinct benefit in the therapy of myocardial infarction. It induces in most individuals peripheral and possibly coronary vaso-dilatation. Incidentally, Heberden demonstrated long ago that alcohol might not only abort but even prevent angina pectoris in many instances if employed in timely doses. In many patients alcohol produces tranquility and relaxation as well as creating a sense of well-being. To obtain the maximum good effect from its use, alcohol should be administered in that form agreeable to the patient. This is often decided by individual taste or preference although occasionally by race and custom. Consider the likes and dislikes of the patient, and do not give it to those who dislike it in any form. Needless to say do not continue to use it when it fails to be of benefit. Discontinue it if the patient becomes depressed under its influence or if it causes gastric hyperacidity or heart-burn. More often, however, some form of alcohol offsets the depression incident to myocardial infarction and its prolonged period of bedrest and disability.

Small doses such as 15 to 30 cc. (½ to 1 oz.) repeated two or three times a day are preferable to larger amounts given once a day. Let me also stress the importance of not giving alcoholic beverages with large amounts of iced, charged water. Whiskey can be given with plain tap water or small amounts of a natural effervescent water; rum in hot, weak tea is excellent and brandy or sherry may be taken straight or in a frappé. Another pleasant drink and food is bourbon whiskey served in an egg-nog made with milk instead of cream. One of the most pleasant effects of alcohol is its sedative and hypnotic action. A glass of wine, sherry or beer, or a "hot toddy" will often prepare the patient for sound sleep. This will negate the need for drug administration and may result

in a night of normal sleep.

Coffee should be prohibited at least during the first week and preferably for the entire illness. It does no good, despite the fact that caffeine is supposed to cause coronary dilatation;^s causes precordial pain; and not infrequently does harm by increasing the nervous tension of the patient or instigating the production of premature systoles.

. Tobacco of any type should be stopped as soon as the diagnosis of myocardial infarction has been made and the patient should discontinue smoking for at least the remainder of the illness. It is harmful and may actually induce attacks of angina in a goodly proportion of patients with this disease. What the underlying mechanism in the heart may be cannot be definitely stated but, judging by the recent report of Wilson and Johnston, it is quite likely to be one of vasoconstriction of the coronary arteries. It would seem, therefore, to be a wise policy to curtail its use at least during the period of bed confinement, although it would also seem the part of wisdom for anyone who has suffered a coronary occlusion to abstain permanently from it.

Diet: A low calorie diet is essential in decreasing the metabolic rate and in turn reducing the demands on the heart. It also prevents the patient from gaining excessive weight during the long period of bed confinement. If the patient is obese the use of a low calorie diet is definitely indicated since the greater the weight, the greater is the work load of the heart.

The diet should be liquid during the first few days with milk or milk with vichy, and warm broths, as the main constituents. These should be given approximately every three hours. Water should also be administered but total fluid intake should not exceed 1500 cc. in 24 hours, particularly if there are any suspicious signs of a failing heart. The Karell diet (200 cc. of milk given every four hours) is often employed during the first few days. Many patients are unable to tolerate the iced fruit juices that are so often given during the early phase of this illness. In fact iced drinks in general had better be avoided. Junket, custard, warm cooked cereal and some of the stewed fruits such as apple sauce and puréed vegetables may be added toward the end of the first week. If the patient is unable to take fluids or nourishment by mouth, particularly if vomiting is present, 50 cc. of 25 per cent glucose solution may be given intravenously twice daily together with 5 to 10 per cent glucose solution by rectum through a Harris drip. Large volumes of fluid,

especially infusions, are contraindicated because of the danger of pulmonary edema. If actual dehydration is present hypodermoclysis may be employed or rectal instillations may be given by catheter or Harris drip, usually 5 to 10 per cent solution of glucose in saline.

During the second and third weeks a more complete diet may gradually be resumed to include some solid foods such as chicken, fish, lamb chops, cooked vegetables without too much roughage, or which do not provoke flatulence, and some of the raw but readily digested fruits. An adequate supply of vitamins should be provided especially during the first week when food intake is restricted. Deficiency of Vitamin B₁ can lead to heart failure or aggravate the degree of failure which may be instigated by the myocardial infarct.

Bowel bygiene: Regulation of bowel function is essential but may be neglected, as a rule, during the first two or three days, particularly if food intake has been limited to fluids. Straining at defecation should be avoided by keeping the stool soft. This may be accomplished by giving sufficient fluids by mouth and the regular administration of 30 to 45 cc. (1 to 1½ oz.) of mineral oil every night followed in the morning by a small enema of oil and glycerine or saline. After the second or third day enemas may be given daily or every second day, if needed, for the next week or so. Subsequently mild catharsis may be stimulated by the use of milk of magnesia or any other mild laxative.

Abdominal distention is sometimes a problem in the early stage of myocardial infarction. Heat applied to the abdomen may give some relief, also the insertion of a small rectal tube. If not successful small turpentine enemas given with care may be employed. Pitressin¹⁰ may be given but with caution since it is a coronary vasoconstrictor. The newer synthetic forms of atropine such as Novatropine or Trasentin are sometimes effective, particularly if distention is secondary to a spastic colon or some other neurogenic state. Small doses of fluid cascara given repeatedly will sometimes relieve distention.

Some modification in bowel hygiene may have to be made after the first week or so for those patients, usually men, who struggle with the bed-pan. A compromise may be made by allowing the use of a commode placed immediately adjacent to the bed onto which the patient may be lifted or slid by means of a special draw-sheet. Needless to say it is to be used only for bowel evacuation.

Management of immediate attack: Control of the severe substernal

pain or distress which introduces most of the attacks of myocardial infarction is highly essential. Nitrites are ineffective. In fact they may do harm and therefore should not be employed. They are especially dangerous if the patient is in shock. Morphine sulphate given subcutaneously in doses of 15 mgm. (¼ gr.) and repeated several times in the space of an hour or two if needed should be administered. Occasionally it fails to provide relief. Although it appears to be the drug of choice in quieting the patient and relieving pain during the period of severe distress and anxiety, it might be well not to repeat it too often since it not infrequently causes vomiting. If the patient is known to be sensitive to this drug Pantopon 20 mgm. (1/3 gr.) or Dilaudid 4 mgm. (1/12 gr.) may be used hypodermatically.

It may be appropriate here to mention the newer synthetic morphine substitutes which are at present only available for investigation purposes but which will probably be released to the profession in the near future. One of the most promising is known as "Metopon" which is a methyl derivative of dilaudid. Its advantages over morphine include less respiratory depression, greater analgesic potency, less liability for producing addiction, and less noticeable emetic properties. Another one is "Demoral" which has recently been investigated clinically at Bellevue Hospital by Batterman. It is a synthetic analgesic approaching the potency of morphine for the relief of pain. Although having a shorter duration of action, it has the advantage over the opiates in not resulting in respiratory or profound cerebral depression. Prolonged use with therapeutic doses has not resulted in primary addiction. Both these new drugs may some day be very useful adjuncts or may even replace the present day narcotics in the treatment of myocardial infarction.

Recently another drug has been advocated during the early phase of myocardial infarction. I refer to atropine sulphate which is supposed to counteract the efferent vagus action which induces reflex constriction in coronary vessels at the onset of attacks of coronary thrombosis. Experimental studies^{13,14} suggest that this action of the vagus may aggravate the cardiac lesion already present and may even precipitate sudden death, probably by initiating ventricular fibrillation. Hence the use of atropine given intravenously in doses of 0.8 mgm. (1/75 gr.) which may be repeated several times daily during the acute stage particularly if pain continues. In the presence of a tachycardia, however, it should be withheld or given in distinctly smaller doses.

The experiments of Manning, McEachern and Hall^{14,15} demonstrated that the ligation of a coronary artery of the dog causes a reflex vasoconstriction of the other coronary vessels. When a coronary artery was ligated under complete anesthesia, there was a low mortality, but if the ligatures were not tied until recovery from anesthesia, there was a high mortality. However, if the vagi were cut or atropine administered before the artery was ligated in the unanesthetized dog, the mortality remained at the same low level as when the artery was tied in the animal in whom the reflexes were abolished by complete anesthesia.

A year ago, during the Graduate Fortnight, Gilbert¹⁶ in discussing "the influence of extrinsic factors on the coronary flow and clinical course of heart disease," referred to some unpublished work, subsequently reported, which showed that the administration of a purine-base vasodilator, such as aminophylline, in addition to atropine, caused an even lower mortality when the coronary artery of a dog is ligated. They have already made use of these observations in the management of coronary occlusion in humans. By the immediate administration of atropine and aminophylline they believe that they have not only greatly reduced their mortality in early cases of coronary thrombosis but the recovery of their patients has been more rapid and more uneventful than previously.

Some authorities^{17,18} use aminophylline alone, others¹⁶ combine it with atropine or papaverine but both administer it intravenously in doses ranging from 0.24 to 0.48 gm. two to three times a day during the acute or critical phase of myocardial infarction. Both groups feel that the results obtained with aminophylline are due to an improvement of the collateral coronary circulation. My own experience with the intravenous use of aminophylline in myocardial infarction, either given alone or with atropine or papaverine, has been rather limited. I have seen satisfactory results in some cases, equivocal or even poor results in others. Although I believe these drugs are valuable in the treatment of an acute myocardial infarct I feel that administration intravenously should be restricted to the critically ill patients rather than given routinely.

If not obtainable in the 10 or 20 cc. ampule, aminophylline should be diluted to this amount with physiological saline, dextrose solution, or distilled water. Injection should be very slow and preferably through a fine gauge needle (22 gauge). Rapid injection may cause fulness in the head or a throbbing headache, vertigo, palpitation, and even precordial pain or oppression. Occasional fainting may take place, especially in sensitive or neurotic patients.^{18,19} Smaller doses such as 0.24 gm. (3³/₄ gr.) should be used in those patients with accelerated heart rates or whose blood pressure is very low, since the drug sometimes causes a fall in blood pressure and/or a tachycardia.

In some patients complete relief of substernal pain or distress is noted almost immediately, even in the absence of an opiate. Reduction in the amount of opiates administered is often possible. It sometimes may be withheld completely when aminophylline or atropine or papaverine are used. However, the latter drugs should not be employed to the exclusion of other important therapeutic measures and should be used with caution and discontinued with the appearance of severe reactions.

Aminophylline may also be given by mouth, preferably in the form of an enteric-coated capsule or tablet to avoid or reduce the gastric irritation which so frequently occurs in those individuals sensitive to the drug or in those patients in whom large doses have been employed. These symptoms include nausea or vomiting, burning epigastric pain, and distention. It may be given orally in doses of 0.2 gm. (3 gr.) three or four times a day for variable periods of time during the first month or two after the onset of the illness and subsequent to the intravenous use of the drug during the critical phase. Gastric irritation may be avoided by discontinuing the drug three to four days at a time, and then resuming for a week or ten days.

There is still considerable difference of opinion concerning the value of aminophylline as a coronary vasodilator both in animals and in man, and especially in the presence of coronary sclerosis or occlusion. Experimental studies in animals^{20,21,22} have given variable, even contradictory, results. In man, however, Levy, et al.,²³ using induced anoxemia in individuals subject to attacks of angina caused by coronary sclerosis, found that aminophylline caused a prolongation of 63 per cent in the time of appearance of pain when given intravenously but only 26 per cent when taken by mouth. Clinical tests^{24,25} controlled by placebos have shown that aminophylline or other xanthines administered orally have no superiority over the placebos. Others have^{26,27} obtained good results with these drugs but employing considerably larger doses. Although the drug is not dangerous when given orally, its intravenous administration is known to have resulted in many instances of reactions, previously men-

tioned, which may be rather disturbing.¹⁸ A few fatalities have been noted but not reported as far as I am able to ascertain. One observer²⁸ believes that he induced an attack of coronary occlusion in two patients with bronchial asthma—one associated with a previous myocardial infarct, the other probably with coronary sclerosis—by using 0.48 gm. of aminophylline intravenously. One of these patients succumbed three months later but no autopsy was obtained.

Fortunately, an appreciable number of patients follow a rather benign course from the onset of their myocardial infarct through to convalescence. Herrick referred briefly to these cases in his first communication in 1912. In these patients the pain not infrequently disappears shortly after onset or even before the physician's arrival and no other severe manifestations of the disease such as shock, embolization, or heart failure make their appearance. Needless to say, in such instances therapeutic measures can be quite limited and intravenous aminophylline or atropine or both are probably of doubtful value or even contraindicated. Overtreatment of the patient in such instances is more to be feared than neglect.

Papaverine: Although not a new preparation, this drug has had somewhat of a renascence, so to speak, in the past few years in the treatment of all forms of vascular disease. It is an opium alkaloid of low toxicity and non-habit forming. It has been shown to be very useful in coronary occlusion, chiefly because it is a powerful coronary vasodilator. Experiments on dogs by McEachern and his Toronto group show that the administration of this drug reduces the mortality resulting from ligation of a major coronary artery. Likewise, the experimental demonstration by Katz, et al. 31 32 that this agent reduces or abolishes induced premature contractions and decreases the ease with which ventricular fibrillation is induced in the dog, suggests the possibility of its clinical value in the treatment of premature systoles, and its use in conditions which are apt to lead to ventricular fibrillation.

As to its mode of action it has been credited by Katz³² with the following effects: A mild sedative action, a definite and lasting coronary dilating action, and the prevention or lessening of the occurrence of premature systoles (auricular, nodal and ventricular) or certain types of rapid heart action like ventricular fibrillation. In this last respect it acts like, but apparently is superior to, quinidine, since it also has a coronary dilating action which quinidine lacks. Furthermore, it is not a

myocardial depressant like the latter drug.

Papaverine, therefore, may be of considerable value in fresh myo-cardial infarction since premature systoles occurring in this process represent an added burden on the heart and may, if of ventricular origin, result in ventricular tachycardia or fibrillation. Relief of pain in this disease has also been obtained by its intravenous use, employing it in doses of 60 to 90 mgm. (1 to 1½ gr.), repeated every two to three hours if necessary. Oral administration can be used to continue its desired effect, the usual dose then being 0.2 gm. (3 gr.) every three to four hours.

Oxygen therapy: In acute coronary occlusion a sudden interference with the flow of blood results in a severe oxygen-want in the myocardium. The use of oxygen in this disease was first suggested in 1929. In the following year and again in 1934 Levy and Barach³³ demonstrated its value as a therapeutic agent in this disease. According to these authorities³⁴ the basis of its use is founded on three facts: (1) "Anoxemia of the heart muscle occurs after sudden occlusion of a sizeable branch; (2) oxygen-want induces impairment of cardiac and respiratory activity; (3) the inhalation of oxygen in high concentration increases the oxygen content of the arterial blood and results in improvement in the functional capacity of the heart."

Oxygen administration in high concentration,³⁵ even in 100 per cent concentration for periods of approximately 12 hours, is particularly indicated in the patient with myocardial infarction who presents circulatory collapse, or severe pain and restlessness which does not respond to the opiates or other medications, and when there are evidences of a failing myocardium. The latter may be suggested by the appearance of cyanosis, tachycardia, gallop rhythm, low blood pressure, dyspnea, and signs of pulmonary congestion. It is also very effective in the treatment of pulmonary edema as a result of left ventricular failure, particularly if given by the positive pressure technique.³⁶ Paroxysmal dyspnea and Cheyne-Stokes breathing also respond to oxygen therapy.

Oxygen tents are capable of delivering and maintaining from 50 to 75 per cent of oxygen. They are comfortable to most patients. The oronasal catheter is simple and efficient but must be carefully placed under direct throat vision. It is said to deliver from 35 to 50 per cent of oxygen. Recently various types of masks have made their appearance including the well-known Boothby mask, both nasal and oronasal types,

which are capable of delivering up to 100 per cent oxygen. They are quite simple, efficient, inexpensive and easily adjusted. However, many patients complain that they are uncomfortable, especially in warm weather. Small face tents are also obtainable, made of transparent plastocele, which fit over the bridge of the nose and may easily be molded to the conformation of the patient's face. This may give oxygen concentration between 40 and 60 per cent. Many patients find this type more comfortable, especially in warm weather than the heavier rubber masks or the nasal catheters.

Complications: More than 50 per cent of the attacks of myocardial infarction are associated with complications and the majority of these occur during the first three weeks. A fairly common one is that of peripheral circulatory failure of some degree which invariably occurs with or immediately after the onset of the attack.

Acute circulatory failure or shock occurs in as high as 1/3 of cases as a complication of the immediate attack. It may introduce the picture in some instances, with pain as a minor symptom or entirely absent, but more often appears simultaneously with the pain. In other instances it occurs hours or days after the onset of pain. Its manifestations usually constitute a classical picture with cold clammy skin, rapid and shallow respirations with frequent sighing, gray, cyanotic pallor of the face which may be drawn and anxious, rapid, feeble pulse and depressed arterial pressure with small pulse pressure. Although a subnormal mouth temperature may be obtained, the rectal temperature is frequently elevated. The cause of this primary form of shock in coronary occlusion remains obscure. Some form of nervous mechanism seems a likely probability. Acute cardiac weakness and failure of the central driving force are undoubtedly contributing factors in the mechanism. A definite decrease in circulating blood volume has been demonstrated.37 This may be the result of stasis in the vascular bed and an increase in capillary permeability secondary to tissue anoxia, and in turn resultant loss of plasma and other blood elements.

If the severe substernal pain which introduces the attack of myocardial infarction is not present during shock, morphine should not be administered unless anxiety and restlessness are prominent because it administered unless anxiety and restlessness are prominent because it depresses pulmonary as well as tissue respiration and thereby aggradepresses pulmonary as well as tissue respiration and thereby aggradepresses the general anoxic state already present. High concentration of vates the general anoxic state already present. High concentration of vates, 75 to 100 per cent, administered by one of the special face masks or by tent should be instituted. Theoretically, vasoconstrictor drugs such as epinephrine should be of some benefit in the shock of myocardial infarction. However, only in rare instances do they seem to be of help. They should be used with caution and preferably in small doses such as 0.5 mgm. subcutaneously or intramuscularly, or 0.1 to 0.2 mgm. of a 1:1000 solution intravenously. Occasionally it is employed much diluted in an intravenous saline drip. It is well known that epinephrine administered to patients with coronary sclerosis readily initiates the anginal syndrome. Hence the caution with which it should be used for shock in coronary occlusion.

I have seen patients with myocardial infarction in shock respond to transfusions of blood or plasma. Such transfusions should be given in quantities ranging from 150 to 250 cc. They probably help by augmenting the decreased circulating blood volume. However, such transfusions should be given slowly in order to prevent overloading the already injured heart. Hypertonic glucose solutions by intravenous infusion may be given slowly in amounts of 100 cc. of a 50 per cent solution and repeated if needed. This may not only increase the circulating volume but also act as nourishment for the heart muscle. It also tends to increase venous return from the extremities to the heart. The intravenous administration of fluids may be hazardous and therefore should be employed with caution. The presence of any degree of heart failure, as determined by clinical or laboratory means (increased venous pressure), is an absolute contraindication.

Elevation of the foot of the bed should be done immediately. The patient should be covered with blankets but artificial heating methods should be withheld since recently some question as to the benefit of artificial heat has been raised. Burns may readily result because the constricted peripheral vessels cannot carry off the excess heat. Then too, if vasodilatation should occur, the blood pressure level will drop further. In addition, excessive sweating may cause further loss of body fluid. Bandaging the lower extremities from ankles to mid-thigh may also be of value. It has been shown that the circulating blood volume may be increased 1000 cc. by this procedure.³⁸

Arrhythmias: Various forms of arrhythmias make up the second commonest complication in myocardial infarction. Some, such as complete heart block and ventricular tachycardia, are quite rare; others, such as premature systoles and paroxysmal auricular fibrillation. are more

common. Probably, most sudden deaths which occur during or after the immediate attack or in the first three weeks are due to ventricular fibrillation. Rupture of the heart is a much less frequent cause of sudden death.

Premature systoles, particularly of ventricular origin, are quite common during the early stage. Those occurring infrequently may be ignored unless annoying to the patient. They can usually be abolished by the use of quinidine in doses of 0.2 gm. (3gr.) three times a day or papaverine 0.2 gm. (3 gr.) every four hours. Either one of these drugs should definitely be used if the premature systoles occur frequently, i.e., once in every ten beats or in series, which suggests that they may be the forerunner of ventricular tachycardia. The latter rhythm has been shown to be the link which connects ventricular premature systoles with ventricular fibrillation.³⁰

I see no justification in the routine administration of quinidine, as has been advocated, during the first two weeks as a prophylactic against the development of ventricular tachycardia or fibrillation. Both disturbances are quite uncommon in patients who survive the first 24 hours, which the majority do. Their onset is commonly preceded by frequent ventricular premature systoles which act as a warning and thereby permit the institution of corrective measures. Ventricular tachycardia is usually amenable to treatment. Also the efficiency of this measure has never been proven and seems rather difficult of proof. Lastly, since quinidine is a distinct myocardial depressant it seems best to employ it only when actually needed.

Ventricular tachycardia is always of serious significance since it may precipitate heart failure, embolism, ventricular fibrillation and sudden death. Although its recognition is only certain by means of the electrocardiogram, its presence should be suspected in any patient with myocardial infarction who suddenly exhibits a rapid rate ranging from 180 to 200 per minute which is basically regular in rhythm. Fortunately, the paroxysm may end spontaneously within a short period after onset. Others, however, continue for hours or even days.

Several drugs are known to influence this rhythm. They include quinidine salts, magnesium sulphate, and potassium chloride or acetate. When quinidine is to be administered, it is well to give a preliminary test dose of 0.2 gm. (3 gr.) by mouth and wait 30 minutes or so to note test dose of sensitivity to the drug such as marked tinnitus, diarrhea if any signs of sensitivity to the drug such as marked tinnitus, diarrhea

or vertigo appear. If not, then doses of 0.4 gm. or even 1 gm. (6 to 15 gr.) may be given at intervals of two or three hours until the bout terminates or signs of toxicity appear. Following return to normal, quinidine in doses of 0.2 gm. (3 gr.) three times daily after meals should be continued for the next week or two to diminish the possibility of recurrence.

Magnesium sulphate may be given intravenously in a 10 to 20 per cent solution in amounts up to 15 cc. It should be injected very slowly, pausing after every 5 cc. to check the heart rate since the attack may stop before the entire amount is injected. It acts by depressing the ectopic focus which is usually the infarct or muscle immediately adjacent to it.

Potassium salts are known to depress the conductivity and excitability of the myocardium. They are also known to potentiate digitalis and quinidine, and finally, when given alone, may abolish premature systoles and paroxysmal ventricular tachycardia. Either potassium chloride or acetate⁴¹ may be employed, using 1 to 2 gm. (15 to 30 gr.) every two to four hours by mouth, until a favorable response is obtained or a maximum of 10 gm. (150 gr.) has been administered.

Another procedure which may be tried, particularly if quinidine or the potassium salts alone are ineffective, is the administration of both drugs.⁴⁰ Quinidine is then given in full doses until 2 to 3 gm. (30 to 45 gr.) have been administered, at which time the potassium salts should be started.

Formerly quinine dihydrochloride was used intravenously to abolish prolonged attacks of ventricular tachycardia and more recently quinidine sulphate. However, the intravenous use of either drug is dangerous because of their severe reaction on the myocardium. Sudden death may occur with both and several such incidents have been reported. Only when all other measures have failed and the outlook appears hopeless would I suggest the intravenous administration of these drugs.

Paroxysmal auricular fibrillation occurred in 12 per cent of an unpublished series² of 200 cases with myocardial infarction at Bellevue Hospital. The majority of attacks are of short duration ending spontaneously. Some, however, continue for days or the rhythm may become established. It is the longer episodes which, as a rule, need treatment since they may, and not infrequently do, precipitate heart failure. The drug of choice in such instances is digitalis given in divided

doses and always by mouth. An initial dose of 0.4 gm. (6 gr.) may be given followed by 0.4 gm. (6 gr.) at intervals of six hours until normal rhythm returns or the ventricular rate reaches 70 or 80 per minute. If sinus rhythm is not obtained by digitalis, quinidine in doses of 0.3 gm. (5 gr.) at intervals of two hours may be employed. If not successful alone quinidine may be supplemented with strychnine sulphate 1.5 mgm. (1/40 gr.) three times a day. This combination has been shown by Smith and Boland⁴² of the Mayo Clinic to be more efficacious in auricular fibrillation than when quinidine is administered alone and smaller doses of quinidine are required if strychnine is also administered. Should fibrillation persist despite quinidine therapy, digitalis may be resumed in maintenance doses of 0.1 gm. or 0.2 gm. once daily.

Congestive heart failure in our experience rarely occurs to any obvious degree in individuals sustaining their first attack of myocardial infarction unless they are 60 years or over, or have a complicating disease such as diabetes mellitus or hypertension.

The clinical signs of congestive failure may not be too obvious as judged by the usual manifestations of dyspnea, pulmonary rales, edema and engorged liver. Venous pressure determinations, however, are frequently elevated even in the absence of symptoms or when only a few basal rales may be the only indication of a failing heart.

The hypertensive cardiac who sustains a myocardial infarct, in contrast to the uncomplicated arteriosclerotic cardiac, quite often develops paroxysmal dyspnea as the prominent clinical phenomenon of acute left ventricular failure. Several therapeutic measures seem effective in this condition. First of all, morphine hypodermatically in a 15 mgm. (¼ gr.) dose should be given immediately. If available, administration of high concentration of oxygen by tent or mask is of value, and if pulmonary edema complicates the picture, it may be given under positive pressure.³⁶

Venesection or phlebotomy may successfully be carried out by the removal of 500 cc. of blood. However, an effect similar to this may be obtained by applying blood pressure cuffs to the extremities and inflating them to a pressure slightly greater than the patient's diastolic pressure. Dramatic relief may be obtained by this means. The purpose is to utilize the peripheral venous system as a reservoir and thereby decrease the circulating blood volume. It has one drawback, it causes venous dilatation and thus may favor venous thrombosis and possibly emboli.

An instrument has recently been devised by Kountz et al.43 which inflates and deflates cuffs, placed on the arms and thighs, in rotation. They believe that as much as an eighth of the total circulating blood volume may be impounded by their method of intermittent constriction. Their application of this procedure in patients with acute left ventricular failure usually resulted in dramatic improvement. They also suggest that acute myocardial infarction is another condition in which reduction of the quantity of blood-flow to the heart might be beneficial in minimizing the demands on the myocardium. In 10 patients with acute myocardial infarction this treatment was given for a period of 14 days. All of them survived, whereas the mortality rate of such patients in a hospital from which a similar group of patients was chosen, was 37 per cent. They state that although a more detailed study must be made before definite conclusions can be drawn, the results suggest that this treatment affords some protection to the heart when the function of the left ventricle is impaired.

Aminophylline, given intravenously in doses of 0.48 gm. (7½ gr.) in 10 or 20 cc. of saline or hypertonic glucose solution, is another drug which is quite effective in acute left ventricular failure. Concentrated glucose solution, such as 50 cc. of a 50 per cent solution, has also been employed alone, particularly when pulmonary edema is present, with seemingly good results.

Mercurial diuretics are of distinct value in acute failure although their full therapeutic action is delayed longer than the preparations and procedures just mentioned. However, because of the recent "wave" of reports in the medical literature^{44,45} of instances of sudden death or severe reaction following their administration, it might be well to stress a few notes of caution:

- 1. Never use more than 2 cc. for the initial intravenous dose. A preliminary dose of 1 cc. intravenously would be preferable for the patient with myocardial infarction.
- 2. Always draw blood into the syringe before injecting the drug and take plenty of time to inject, employing a small calibre needle (25 gauge).
- 3. Check the patient for evidence of salt depletion. If present give sodium chloride for one or two days prior to the administration of the diuretic.
 - 4. If the patient has been taking digitalis, be certain that the digitalis

dosage is well below the toxic level, or discontinue it for a day or two. It might be well also to use a small dose, i.e., 0.5 cc. to 1 cc., at the initial injection intravenously. Larger doses can be given later if satisfactory diuresis does not result.

Mercurial diuretics may be used rectally in suppository form; more recently a tablet has been offered for oral use. Neither one is as effective as the intravenous or intramuscular preparations. All forms of mercurial diuretics are made more effective by the administration by mouth of ammonium chloride, ammonium nitrate or potassium chloride, preferably given in enteric-coated capsules.

Although it is of distinct importance to call attention to the dangers of these diuretics it seems just as important not to exaggerate these dangers since these preparations constitute one of the most valuable groups of therapeutic agents in the treatment of diseases of the heart. As DeGraff⁴⁶ has stated, one must remember that the toxic reactions and deaths reported from mercurial diuretics are in reality only a very small number in relation to the extensive use of these drugs. These reports, therefore, should not discourage the rational use of these diuretics.⁴⁷

Digitalis. I have purposely left this drug to the last because of its disputed status in myocardial infarction. As a rule digitalis is not needed in the immediate treatment of paroxysmal dyspnea with or without edema since the therapy just outlined is usually effective. However, since this mechanism is indicative of left ventricular failure it may be desirable in some instances to follow the administration of the rapidly acting drugs by digitalis with the hope of maintaining the patient's cardiac reserve.

Indications for the use of digitalis in myocardial infarction include (1) the appearance of progressive congestive failure, either with or without preceding left ventricular failure, which has not responded to the administration of mercurial diuretics, fluid intake restrictions, sedation, or high concentration of oxygen, and (2) the control of paroxysmal auricular fibrillation, particularly the attack with a rapid ventricular rate or that which is complicated by signs of congestive failure.

I would suggest that digitalis should always be given in such cases by mouth or by rectum and never intravenously. Dosage should be smaller than in the average cardiac and given more cautiously with careful supervision during administration and frequent check-up for early therapeutic effect or toxic signs or symptoms. I would advise the general practitioner to use the tablet of U.S.P. powdered digitalis leaf in the patient with myocardial infarction rather than any of the new digitalis glycosides, at least for the present. Goodman¹¹ of New Haven pointed out in a recent lecture at the Academy that in the overwhelming majority of patients with heart failure one will find this preparation easy to administer, readily absorbed when given by mouth, effective in its action on the myocardium; also that it possesses an adequate amount of safety, is stable in potency, and cumulation and elimination occur in the body at rates allowing complete digitalization at varying speeds and satisfactory maintenance of desired therapeutic effects for long periods of time. Undoubtedly Doctor Gold will discuss this problem in detail in a subsequent lecture.

The fear of cardiac rupture in myocardial infarction due to digitalis therapy has been highly exaggerated. It may interest you to know that in a large series of myocardial infarcts with rupture reported from the Pathological Laboratory of Bellevue Hospital. none of the individuals had received digitalis.

The other fear has more to substantiate it, namely, to instigate an arrhythmia due to the irritability of the injured myocardium. I believe this is a likely relationship although once again let me remind you of the appreciable number of patients who spontaneously, without digitalis administration, develop rhythmic disturbances including ventricular tachycardia and ventricular fibrillation. Therefore, I again repeat that if the drug is indicated it should be administered but with caution and careful supervision.

Embolism. This occurs in 12 per cent of cases of myocardial infarction.² It usually takes place during the first six or eight weeks. The source of the emboli is usually the mural thrombus in the left ventricle which commonly forms on the endocardial surface of the infarct. Some day it may be demonstrated that this will be prevented by the use of an anticoagulant such as heparin or dicoumarin. Emboli may lodge in any part of the systemic or pulmonary circulation, depending on the site of origin, but the brain, the peripheral arteries of the extremities, and the lungs are the most important sites. Pulmonary emboli are apt to occur later, after the third week, since their source is usually not in the heart but in the veins of the pelvis or lower extremities. Here throm-

bus formation is initiated by the prolonged inactivity of the patient and other concomitant factors. Large emboli breaking off from these sites are occasionally the cause of sudden death during the course of myocardial infarction.

The treatment of choice includes immediate intravenous papaverine in large doses, 0.1 to 0.2 gm. (1½ to 3 gr.), repeated in two hours if needed. 40,50,51 This drug may bring about a rapid return of color and function to the affected extremity accompanied by disappearance of pain. It may also be useful in cerebral embolism and very definitely so for pulmonary emboli. When the extremities are involved, paravertebral sympathetic block is another beneficial measure in some cases in reducing vasconstriction of collateral vessels as well as in major vessels. Embolectomy is probably too dangerous in the presence of fresh myocardial infarction because of the bad operative risk in these patients. However, Pratt⁵² believes that embolectomy is indicated in every instance when the diagnosis is made, even though an occasional patient will survive without the removal of the embolus.

Diabetes Mellitus. That coronary occlusion with myocardial infarction is not an infrequent occurrence in the patient with diabetes mellitus is common knowledge. It also is generally known that caution must be exercised in the use of insulin in this combination of diseases. Although glycosuria and hyperglycemia may be treated conservatively in such instances, acidosis cannot, since it may cause death. Nevertheless, some 53 feel that insulin should not be used in the presence of coronary thrombosis since it is said to place an added burden upon the heart and may cause hypoglycemic shock, acute coronary insufficiency, or even death. Having seen several patients with myocardial infarction needlessly go into diabetic coma because insulin was withheld, I am rather adamant in stating that this drug should not be withheld, if needed, even when diabetes is complicated by coronary occlusion. Obviously both the dietary regime and insulin administration in these patients should be modified. This may be done by reducing each individual dose but, if necessary, increasing the number of injections so as to avoid hypoglycemia and yet be sufficient to prevent acidosis.

In some unpublished experiments performed by Ralli,⁵⁴ diabetic patients in the arteriosclerotic age period, including some with a diagnosis of coronary sclerosis, were given insulin in divided doses sufficient to prevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hypotoprevent hyperglycemia and glycosuria but not enough to cause hyperglycemia and glycosuria bu

glycemia. Serial electrocardiograms were taken frequently during the course of administration. In none were there any obvious deviations from the normal.

As Joslin⁵⁵ has recently emphasized "diabetic coma is an acute deficiency state, a condition in which the primary disturbance is a lack of insulin." He also states that "when a patient with diabetes is seen in diabetic coma it is proof that someone has blundered and, if death due to diabetic coma occurs, the rule still holds." I should like to add that this holds true even when the patient has a complicating coronary occlusion.

It apparently is wiser to use regular insulin in patients with myocardial infarction since severe insulin shock seems more apt to occur with protamine zinc insulin.⁵⁶

In closing I merely wish to say that I have only touched on what I felt were the highlights of the problem assigned to me for discussion.

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CISCOSCIONIS OF FELLOWS OF FELLOW

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APRIL, 1943

THE PRESENT STATUS OF SHOCK THERAPY OF MENTAL DISORDERS*

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this paper is not an easy one, and the selection and presentation of the facts now available constitute difficulties which are not satisfactorily surmounted. On the one accumulated from the great variety of viewpoints and experiences in vogue would be far from enlightening since statistical treatment of doubtful material is seldom if ever helpful; while on the other hand a comprehensive, detailed description including all that is pertinent in the now-extensive field of shock therapy would be too extensive to present in a short treatise.

For the past five or six years the pharmacological shock therapies have dominated psychiatric research with their main focus in schizophrenic disorders. They have also infiltrated other branches of medicine. During the year 1941 and what has passed of 1942, some one hundred fifty-seven published articles on the action of insulin, metrazol, electric

^{*} Presented October 21, 1942 at the fifteenth Graduate Fortinght of The New York Academy of Medicine.

currents, and other shock producers, have appeared in the scientific literature of the world. Of these fifty dealt with the effects of the convulsant, metrazol, forty-eight with electroshock methods, sixteen with insulin, and forty-three with other coma-producing drugs and procedures (nitrogen, sodium amytal, and combinations, etc.) Only a few of the most recent pertinent contributions can be mentioned in this paper.

Although this is sufficient evidence to show that a great deal of work has been done and is still going on with the shock methods, these published reports present a discordance in the results obtained. There is as yet no consensus on the basic value of any of these treatments, some authors being very enthusiastic over their results, others being unconvinced of favorable results, and still others expressing frank opinions on the inadequacy and even harmfulness of such procedures. One thing is certain, shock therapy is receiving an extensive clinical trial as it has been widely adopted in mental hospitals of all kinds, in general hospitals, in out-patient departments and clinics, and in private offices of general practitioners, as well as in those of psychiatrists.

There is a sufficient skepticism among this horde of workers to insure a careful investigation and testing of the numerous problems and questions which have been raised and to promise some more reliable information about several all-important items. Experienced psychiatrists are concerned with the following questions on which there are positive opinions supporting both sides based on reported experiences:

1. Will shock treatment finally go the way of many, if not most, other "cures" which have had their period of popularity and enthusiastic support only to be discarded as not worth pursuing further? The history of the treatment of schizophrenia illustrates particularly the significance of this question.

2. Is this treatment a specific? Does this radical approach offer any lasting benefit? This question recurs in the minds of those psychiatrists who note that patients go from one hospital or sanitarium to another receiving different kinds, degrees, and "courses" of shock therapy without any tangible lasting results. Are these patients exceptions or are relapses always to be expected?

3. Is the treatment being applied improperly, inadequately, or dangerously by many hospital staffs and private practitioners?

4. Does it aid the patient to understand his personal problems and

does it help the psychiatrist to understand the patient, his disorder, his problems, or his constitutional equipment?

- 5. Does it tend to discourage organized beneficial psychotherapy in general and to encourage neglect of the same in individual patients in particular?
- 6. Which type of shock therapy is the most efficient and under what circumstances, and for what disorders is a special therapy selected? Is electric shock the most efficient in certain disorders or is its growing popularity and preference based on its relative simplicity of application, its after-care advantages, and its inexpensive features as compared to insulin, for example?
- 7. Does the danger of damage to the body structures, and to the brain in particular, outweigh any benefits that might be obtained by any of these treatments?

While there is as yet no satisfactory answer to many of these questions, some comments regarding them based on reports, experiences, and experiments are in order. Discordances in results and findings in any scientific work indicate the necessity of additional investigation and suggest that there is some lack of uniformity in the selection of material, in the technical procedure, or in the interpretation of the results, particularly as to what constitute "cures," recoveries, remissions, improved, and so forth. It is rather obvious that this is the case with shock therapy.

Regarding the indications for treatment and the selection of patient material for the application of shock methods, some believe that in order to test the efficacy of the treatment patients should be selected for whom the prognosis seems to be hopeless, and who have resisted all other forms of therapy; others have treated everything from character disturbances and mild neuroses to severe psychoses with organic brain diseases, not omitting a try at general paresis.¹

It should be emphasized that all of our classifications of knowledge, including those of mental disorder, are constructed by man out of his impressions and are not necessarily made so by nature, therefore they may not be valid and are probably at best only temporary in significance. There is no distinction in nature between "organic" and "functional," a concept which is man-made and probably does not actually exist biologically. As far as our knowledge of correlations is concerned, there seems to be a greater gap between "anatomical" and the "physiological" than between the "physiological" and "psychological." The

TABLE I
COMPARATIVE RESULTS WITH DIFFERENT METHODS

| | Insulin . | Metrazol | Electroshock | |
|----|---|---|--|--|
| ı. | Catatonic dementia pre- cox | Involutional melancholia | Involutional melancholia | |
| 2. | Paranoid dementia pre- cox | Catatonic dementia precox | Manic - depressive psycho sis (depressed phase) Catatonic dementia preco | |
| 3. | Hebephrenic dementia precox | Manic - depressive psychosis (depression) | | |
| 4. | Involutional melancholia | Other depressions | Manic - depressive psycho sis (manic phase) Other depressions Psychoneuroses | |
| Б. | Manic - depressive psy- chosis (depressive phase) | Manic - depressive psycho- sis (manic phase) | | |
| 6. | Manic - depressive psy- chosis (manic phase) | Psychoneuroses | | |
| 7. | Psychoneuroses | Paranoid dementia precox | Paranoid dementia precox | |
| 8. | Simple dementia precox | Hebephrenic dementia | Hebephrenic dementia precox | |
| 9. | Alcoholism | precox | | |

manner in which structure performs its physiological functions is not more thoroughly understood than is the physiological-psychological relationship.

Regardless of the uncertainty and lack of uniformity in diagnostic schemes and classifications, an analysis of the literature and Kolb's² (1942) comprehensive survey of 305 mental hospitals show a certain amount of consensus on what types of cases may be treated with a preferred shock method, with some expectation of success. The indications in diagnostic terms, and in order of the frequency of success with the three main shock therapies, are presented in Table I.

Combinations of insulin and metrazol, and of insulin and electroshock, are used and are given preference by many workers, but speaking generally the results have created a choice of insulin for dementia precox (or schizophrenia), and the convulsion-producing methods, metrazol and electric current, for involutional and other depressions, including those in the manic-depressive syndrome.

Psychoses called "dementia precox" and "schizophrenia" have received a great deal of attention and may serve as examples demonstrat-

ing some of the reasons for a lack of uniformity in therapeutic results. It was long considered erroneously as a hopeless disease. The large number of new cases developing each year seems to have obscured the fact that remissions were not infrequent before the era of shock therapy. According to reports, Sakel's insulin method has produced as high as 70 per cent remissions.

'At practically all psychiatric clinics the diagnosis of "schizophrenia" is made as a collective affair which includes a number of clinical pictures so atypical as to suggest an entirely different genesis. These atypical or pseudoschizophrenic forms compose the majority of "schizophrenic" patients treated in some clinics. Herein may lie the difference in reported clinical results which are certainly more favorable in the pseudoschizophrenic forms than in the genuine nuclear types, and they cannot serve to test the value of any method of treatment to be interpreted in terms of the whole category of schizophrenia. Clinically they may resemble atypical depressive and manic states, or show alternating conditions of excitement and stupor with affective trends, or have projection symptoms (often called "paranoid") that are compensatory but not deeply seated and need not be nuclear in nature. In studying the effect of therapy, it would be highly desirable and advantageous to separate these conditions from the main group and designate them as atypical schizophrenic reactions.

Whatever it is that releases a latent schizophrenia in an individual, whether it be in an endocrine setting, a metabolic dysfunction, an exogenic intoxication, an infection, or a psychogenic trouble, it seems logical that the character of the onset, the nature of the symptoms, and the final result depend upon both the qualitative and quantitative relationship between the product of the chromosomal components and the precipitating factors. Studies of the individual over a number of years, which include the prepsychotic character, the intellectual status, the social and physical disease factors, the bodily form, and the onset and course of the psychosis have given us some pertinent information on what varieties of reaction tend generally toward recovery, remission and improvement, and those which tend in the direction of a poor prognosis regardless of the type of treatment applied, if any, of a special nature.

Bleuler, who was a master observer in this field, found that schizophrenia in which catatonic features developed gradually offers a bad prognosis; moreover it is our experience that cases of typical catatonia without paranoid components or other mixtures have an unfavorable prognosis and retain most of the expressions of the disorder throughout the course, a fact which we interpret as characteristic of an organic disease, systemic in nature. Schizophrenic psychoses comparatively poor and colorless in symptoms have an unfavorable prognosis unless the person is of a low order of intelligence in which case the prognosis is much better. Kretschmer emphasized that the asthenic body form is not only highly predisposed to schizophrenia but also carries a poor prognosis regardless of the type of therapy employed. However, remissions do sometimes occur in those with typically asthenic habitus and schizoid personality. Schizophrenia precipitated by psychic trauma yields an unfavorable prognosis if there is a prepsychotic personality characterized by stubbornness, inelasticity, and constriction of interests; however, if the trauma occurs to one with a rich personality with many interests, recovery is common.

In contradistinction to the varieties just mentioned those patients, whose psychoses begin with an atypical acute phase, or who have a pyknic habitus, a cyclothymic temperament, or prominent exogenic causes, or some combination of these, have a definitely favorable prognosis. Among the unfavorable outcomes the pyknic habitus has been more rare, while cyclothymic temperaments are more frequent; therefore they do not always occur together, as is sometimes assumed. Of the two the pyknic habitus seems to count for more than the cyclothymic temperament in evaluating the prognosis. Additional research may reveal which is of the greater significance for the prognosis, the body constitution or the kind of temperament. A combination of pyknic habitus with cyclothymic temperament and depressive features in the symptomatology of the acute phases of the psychosis is often present in the remitting cases, also exogenic traumas, or precipitating factors prior to the onset of the disorder, have been relatively numerous. Among these have been alcoholic abuses, thwarted love affairs, unemployment conflicts, operations, head traumas, family conflicts, and child-hirth.

In some instances after "improvement" or "social recovery," the mental status of the patient remains the same for several years showing only slight or perhaps concealed oddities and mild disorders of thinking. He may retain a number of the symptoms of autism and constricting.

tion of ideas, but these have become isolated, influencing his daily behavior very little. He has adjusted himself to the world with personality well preserved and capable of making his living. He is usually classified as "cured" and may be so considered by those about him.

All of these natural and sometimes spontaneous reactions toward improvement and recovery, with their compensatory features, must be kept in mind while evaluating the results of shock therapy. Shock therapy may and apparently does exert a favorable effect upon this tendency to get well, and it has been the experience of most workers with these methods that hallucinations, mild paranoid ideas, and borderline symptoms tend to disappear, at least temporarily.

Other sources of discord in estimating end results are the time allowed to elapse between the end of the therapy and the final examination; and the lack of much-needed follow-up studies. Some results are reported immediately after the completion of the treatment while others report at various post-treatment intervals.

Some valuable, careful follow-up studies were made by Bond³ on 125 insulin-treated schizophrenic patients and 153 consecutive schizophrenic patients for controls at the Institute of the Pennsylvania Hospital in Philadelphia (1941). Here the use of insulin has been followed by immediate and important gains in one-half of all patients, and in about two-thirds of the acute cases of less than eighteen months' duration. After two years these gains were maintained in only one-fourth of all patients, and in about one-half of the acute cases. Similar gains were noted in one-sixth of the control cases, two years from the time of admission and without relation to the previous duration of the illness. Bond's experience indicated that while insulin shock is strikingly effective in schizophrenia, there is need for supportive measures to hold these gains which appear quickly but tend to disappear. Such studies are necessary and are long overdue from many clinics where the treatment has now been used for several years.

Cheney and Clow⁴ in 1941 reviewed results in 50 cases of dementia precox from six months to two and one-half years after insulin, thus gaining some impressions of prognostic value. According to these authors, the most favorable outlook is in men under 30 years of age who have the history of a comparatively adequate prepsychotic personality, whose psychosis had an abrupt onset with a definite external precipitating cause, an illness of less than one year's duration, and the sympto-

matology of an excited catatonic state without evidence of deterioration. Those least likely to benefit are women over 32 years of age with adequate personalities, insidious onset, no definite external precipitating causes, who develop mixed clinical forms with evidence of deterioration and with the disorder usually of more than one year's duration. Various combinations of these prognostic factors occurred in different patients, but their relative predominance influenced the outcome. Patients who were to improve usually showed this relatively early in the course of treatments. If the results did not appear early a prolonged course of treatment rarely produced recovery. Previous attacks with remissions did not seem to influence the outcome.

Patients who will benefit by insulin therapy have the same characteristics as those formerly improved by other forms of treatment. This may indicate that insulin has no specific curative effect but accelerates or facilitates improvement in those who have the constitutional or innate capacity for improvement. Cheney and Clow believe that it should be supplemented by psychotherapy and occupational therapy. In their series, the results indicated that a 16 per cent recovery rate may be expected after intensive treatment with about one-half of those to remain benefited after 6 months to 2½ years. The treatment if confined to favorable cases, however, may result in an improvement rate of 90 per cent at the end of the insulin course, and of 80 per cent at the end of 6 months to 2½ years.

The results to be expected and the degree of extension of the therapy justified will depend eventually upon an accumulation of follow-up and comparative studies of this character. The more recently developed electric shock method is now in the front ranks for preference in treating certain mental states and our comments on the present clinical aspects must be brief and center around a few of the most important features.

A recent (1942) report by Hemphill⁵ on his experiences with 200 cases can be used as a sample investigation. This series contained 137 women and 63 men, and I have taken the liberty to arrange his results in Table II, using his own diagnostic terminology:

Thus the results were highly satisfactory in the depressives and manics, i.e., the affective disorders, and the author emphasized this particularly for involutional melancholia which was included with the "deticularly for involutional melancholia which was included with the "deticularly for involutional melancholia which was included with the "deticularly for involutional melancholia which was included with the chronic pressives"; but results were very poor for the schizophrenics, the chronic

TABLE II

| | Recovered | Improved | Improved in Hospital | Unimproved |
|-------------------|-----------|----------|----------------------------|------------|
| Depressives | 35 | 6 | 0 | 4 |
| Manics | 14 | 2 | 2 | 1 |
| Schizophrenics | 4 | 8 | 26 | 76 |
| "Mixed" psychoses | 4 | 3 | 0 | 4 |
| Psychoneuroses | 2 | 4 | 1 | 4 |
| | | | | |
| | 59 | 23 | 29 | 89 |

patients showing social recovery rather than a more complete restitution. The effect was a little better in the more recently developed cases. Hemphill in generalizing stated that the best results were obtained by three convulsions weekly, and that the recoverable cases usually showed some improvement before the fifth fit. He warned that physical illness, sepsis, and prophylactic inoculations within 48 hours of treatments are contraindications, and also there is a possibility of reactivating pulmonary tuberculosis.

It has been noted that in Hemphill's report poor results were obtained with his group of patients diagnosed as "schizophrenics." In contrast with these poor results one should mention the investigation of Kalinowsky and Worthing* who found that electric shock alone may be of great benefit in the production of remissions in early cases of schizophrenia and provided that the series of convulsions is of sufficient length. When broken down the material illustrates emphatically the importance of early treatment in schizophrenia, and on the basis of our personal knowledge of this work one should state that the sufficiently long series of treatments is of great importance. The results of these authors also show that as the duration of the illness increases a much smaller percentage of remissions occur.

Impastato and Almansi⁶ (1942) among others have insisted that the patients should be studied carefully neurologically, roentgenologically, and biochemically, in addition to having electrocardiographic and elec-

^{*} Psychiatric Quarterly, 1943, 17:144.

troencephalographic evaluations in connection with the treatment. They refer to the impression, however, that the anxiety and tension due to the mental disorder may be worse physically for the patient than some of the supposed "contraindications." For example, in diseased heart conditions the convulsion may be less damaging than the constant tension due to anxiety and depression. At any rate, cardiac patients have been treated successfully and so have those with hypertension, as well as those who have reached the 70 year level or above with circulatory systems showing evidence of senility and arteriosclerosis.

Clinically there are several interesting points among which are the instantaneous relaxation, the reduction of all external stimuli, the lessening of internal tension characteristic of several mental disorders, and the amnesias that follow the seizures which persist for some time in various degrees. These seem to operate therapeutically with the amnesia aiding the patients to forget their emotional problems temporarily and thus eventually breaking up the psychopathic pattern. In the successful case the patient has gained a more complete control over the dominating psychopathologic ideas, and the immediately favorable results are startling, even miraculous at times in the involutional melancholias, agitations and other depressions.

In general the results of electric shock therapy may be little if at all superior to those reported following metrazol, but there is a growing preference for the former method. Some of the reasons are: (1) the technique of application is much simpler and there is no problem of inaccessible or thrombosed veins; (2) a convulsion is practically always produced which is less violent and of shorter duration; should the fit fail to develop there is seldom excitement; there is rarely any post-convulsive excitement and fewer post-treatment convulsions have been reported; (3) unconsciousness always and usually amnesia for the treatment are produced; there is no pain, rarely disagreeable sensations, few or no unpleasant memories, rarely fear, and no feeling of dissolution and death which is apt to appear in the metrazol picture; and (4) complications are less common; it is less dangerous in organic conditions; there are fewer vertebral compressions; and the death rate is not as high as that reported for metrazol.

The method is less expensive and more easily applied than the other shock therapies, and perhaps herein lies the danger. It is actually a rigorous, major procedure following which unexpected things sometimes

occur, such as panic over the memory disturbance which, by the way, may remain over a long period in some cases, confusional episodes, and excited states. For these reasons and other possible complications it is desirable to carry out the therapy under the protection of a hospital environment, in fact the physician who does it outside the hospital or without an equivalent protection for the patient is assuming unnecessary, as well as unwise, responsibilities.

The most commonly mentioned complications of a physical nature following shock therapy are cardiac and other circulatory disorders including cerebral vascular accidents, pneumonia (aspiration and bacterial), activation of tuberculosis, lung abscess, fractures and dislocations, sore back, and memory defects. This array of possibilities should convince anyone that we are dealing with a radical form of therapy and one that should be as carefully applied and controlled as possible. Occasionally death results either directly or indirectly. Kinsey⁷ (1941) reporting on all published cases found the incidence of death to be 73 per 10,000 patients treated with insulin, and 23 per 10,000 treated with metrazol. Classifying these deaths under cerebral, cardiac, and pulmonary causes, the order of frequency was as follows:

Cerebral —Hypoglycemic encephalitis (insulin) (38 of 90 deaths)
Status epilepticus
Hemorrhage and edema
Embolism (metrazol)

Cardiac

Pulmonary—Aspiration pneumonia
Other pneumonias
Abscess of lung
Tuberculosis

As the brain is the most sensitive structure of the body, one wonders whether the application of these powerful measures does not result in some irreparable damage. There are a number of histopathological investigations bearing on this question from both human and experimental animal material. In human brains from those dying after insulin therapy, Ferraro⁸ (1942) found zones of rarefaction in various cortical areas due apparently to the gradual disappearance of affected nerve cells, as well as the absence of cells in patchy, focal areas where they had undergone degeneration and disintegration. There were areas of cortical devastation involving various layers with disturbed cortical cy-

toarchitecture particularly in the frontal and temporal areas and in the purkinjian layer of the cerebellum.

The so-called "toxic" reaction characterized by acute swelling and chromatolysis, which is reversible to some extent, is common. There are also ischemic changes in the cells in the region of the blood vessels. Fatty degeneration of the neuron is common and there is an increase in intracellular lipoids particularly in the temporal lobes according to Kobler⁹ (1938), Kastein¹⁰ (1938), Terbrüggen¹¹ (1931), Ferraro and Jervis¹² (1939). There is some question as to whether this is a non-specific reaction in toxemia or the result of a specific action of insulin upon the intracellular metabolism of lipoids. Rivore, Staub, and Asher have pointed out that sugar under the action of insulin may release fatty substances in the tissues. Kobler⁹ and Malamud¹³ (1938) maintained that insulin probably has a damaging effect upon nerve cells, and Holmes¹⁴ (1930) thought that insulin diminishes intracellular oxidation in the brain.

The blood vessel changes were described at length by Ferraro⁸ (1942). They are productive in nature consisting of proliferating changes of the intima, and hyperplasia and swelling of the intimal endothelial cells. This vascular proliferation may be related directly to insulin intoxication as the change is similar to that reported numerous times by investigators as due to various other toxins such as lead, organismal toxemias, and infections.

At Northwestern University, Weil and Liebert ¹⁵ (1940) studied the brains from six mental patients who died 2 to 10 months after treatment with metrazol injections. The outstanding hospitalization features were marked hypertrophy and hyperplasia of astrocytes, and, to a lesser degree, the microglia. Disease of the ganglion cells was less pronounced. In the case of more recent illness (two to three years' duration), the reaction was more pronounced than in those of five to ten years' standing.

Arieti¹⁶ (1941) at the New York State Psychiatric Institute made histopathologic observations on 5 monkeys after metrazol-induced convulsions. Histopathologic changes were not always present in the central nervous system. Moreover when they did occur they were not proportional to the number of convulsions, dosage of the drug, or the duration of the seizures. The alterations were mild, more so than those described as due to insulin treatment. There were usually small groups

of neuron cells showing acute degenerative changes, but some revealed the severe type of degeneration described long ago by Nissl. Anemia of the external cortical layers, anemic and hyperemic foci in the inner areas, and general breaking up of the network of capillaries of the brain were also noted. Interstitial and parenchymatous involvement of the kidneys were always found.

Regarding the action of the electric shock, Löwenbach and Stain-brook¹⁷ (1942) state: "A generalized convulsion leaves a human being in a state in which all that is called the personality has been extinguished. Although the autonomous functions are operating more or less regularly, the individual does not react for a while to any kind of stimuli and the activity of the cerebral cortex as revealed by the electroencephalogram has completely ceased. The convulsion is succeeded by a phase during which the higher functions return and in which the personality is reintegrated. It seems as if the subconvulsive reaction does not differ from the convulsive except in degree, but in these minor reactions where the brain has not been completely exhausted reintegration may begin at any level, and the recovery may be much more quickly and indeed sometimes imperceptibly achieved."

The extensive use of electric convulsion treatment in the psychoses makes it imperative to ascertain what happens to the brain during or after such applications. It is a matter of great practical importance that we gain some knowledge of what is responsible for the confusional state and the amnesia following the treatments, and particularly as to whether these states are due to some form of structural damage. If the electric current has damaged the brain permanently there have been but few clinically demonstrable ill effects when the specified doses and the proper adjustments have been carefully followed, but this form of treatment should not be used without the utmost discrimination and caution until more is known about the possible danger to the nervous system.

Alpers and Hughes¹⁸ (1942) studied two cases treated by electroshock. One patient dying after 62 convulsive treatments revealed fresh hemorrhages in the cerebral cortex, white matter, and brain. The brain of the other patient who died five months after the final treatment showed old areas of perivascular damage mainly in the white matter. These lesions seemed to be due to the convulsions and the question was proposed as to whether these changes might persist indefinitely. The perivascular areas in some parts of the brain may be capable of produc-

ing some types of sequelae.

Subarachnoid and punctate hemorrhages in the brains of cats subjected to electrical convulsions were described by the same authors¹⁹ (1942); no lesions had developed in the pons and medulla. Similar findings were reported by Heilbrunn and Weil²⁰ who treated rabbits and rats in keeping with the procedures used with humans. No generalized ganglion cell lesions or generalized proliferative glial reactions were observed but there were changes in the venous system in practically all cases (25 out of 28). Hemorrhages were present in the meninges and in the substance of the brain and spinal cord. These hemorrhages were confined to the perivascular regions of the capillaries, being caused by rupture of the walls.

Changes in the electrical activity of the brain as demonstrated by Pacella, Barrera, and Kalinowsky²¹ (1942) indicate that there is an immediate change in the cerebral physiology somewhere, but the nature and degree of any permanent pathological change have not been definitely established. An insufficient number of cases have been examined pathologically and as far as the human material is concerned any examination of the brains from those dying during or after the treatment must differentiate as to which lesions, if found, are due directly to the action of the therapeutic measure, which are caused indirectly by various somatic-physiochemical processes released by the therapy, and finally which are produced by other processes and bodily lesions playing a major role in the lethal event. The brain must be examined in the light of all other postmortem findings and conditions in the body before any final evaluation can be made in a given case, as the brain participates in many lethal conditions the foci of which lie in the other organs of the body.

Conclusions

1. Insulin, metrazol, and electroshock with the adjuncts that have been recommended by some workers are all valuable in proper hands and particularly when they are supplemented by systematic psychotherapy and other measures available in psychiatric clinics. In some instances they have undoubtedly been misused. They are not a panacea for all mental disorders. Superintendents of mental hospitals and practicing physicians have had numerous requests to apply these treatments to the mentally defective, the aged, deteriorated patients, and others

entirely unsuitable in every respect. Such requests, often leading to unpleasant controversies, are due usually to the false hopes aroused in relatives and friends by startling statements in the press and the inaccurate reports in the numerous recent books on psychiatry written by enthusiastic laymen who, with all good intentions, peddle misinformation.

- 2. At the present time there is no theory as to the nature of the shock reactions sufficiently comprehensive to be taken very seriously. Theories not susceptible to experimental examination are hardly worth discussing. There is as yet insufficient knowledge to justify attempts in the direction of theory building. Serious efforts to sort out existing knowledge with the expectation of making some sound deductions may be made so that in time a comprehensible formulation of the fundamental elements in the problem will be possible.
- 3. If statistics on insulin therapy are taken as indicative of therapeutic results in schizophrenia, every possible stated percentage of "cures" can be found from Sakel's 70 per cent to Langfeldt's experience of "no cures" in the clear-cut nuclear cases. It is probable that 70 per cent of satisfactory remissions would not be unusual in those clinics where the material is composed mainly of the atypical varieties of schizophrenia. When the diagnosis is just "schizophrenia," results up to 60 per cent "recovered" or "improved" by means of any therapy do not indicate the relationship between that therapy and the disorder. This situation demands complete and accurate information, first, as to the form of schizophrenia, second, as to the special characteristics of the individual as a patient, and third, perhaps above all, as to the factors which will make possible the establishment of criteria for "recovered," "social recovery," "improved," "not improved," and so on, which will replace the present chaotic state of affairs in this respect on which statistics are prepared. Only precise statements and careful differentiation of cases can contribute toward bringing the problem to a point of national and international coöperation for solution. The same applies to mental disorders other than schizophrenia.
- 4. Possibly the shock methods should be used only as adjuncts in a total therapeutic approach, including psychotherapeutic interviews with the physician, physiotherapy, occupational therapy, physical education. and a program to promote socialization.
 - 5. It is as yet too early to make any final pronouncement on the

results of electric shock therapy in the treatment of various mental disorders. Premature announcements of results may often be prejudicial to a proper evaluation of any method of therapy, either because of the utilization of an insufficient number of cases or because of selective factors entering into the determination of the types to be treated. Technical advances are also always under way to modify the picture. It is interesting to note that there are neurologists and psychiatrists who, without any extensive personal experience with any shock therapy, are nevertheless actively opposed to all shock therapies on theoretical grounds.

6. Electrically induced convulsion therapy appears to be a safe and convenient method of treatment in mental disorders. It is particularly satisfactory in the affective disorders and especially in "involutional melancholia," but it cannot as yet be regarded as a specific. Its value in chronic schizophrenic illnesses is more of the nature of promotion of social improvement than fundamental changes. Its effect on recent cases is much more favorable, and early treatment is well worth trying. Some workers have better results in schizophrenia when a comparatively large number of convulsions are given, the general tendency being to afford too few to promote a successful outcome.

7. So far there is no reason to emphasize any particular contraindication for electric shock therapy which does not already exist for

any other form of shock treatment.

8. Combinations of the various types of shock therapy may be particularly valuable in certain cases as it does not follow that if one method, insulin, for example, fails to produce a favorable effect, some other method, such as metrazol or electric shock alone or in combination with insulin, will not produce good results.

9. The shock therapies are safe clinically if handled by individuals properly trained in their administration and in the handling of psychiatric patients. Mental confusions and other psychiatric emergencies will arise demanding expert attention and the psychiatric amateur may find

himself at a serious disadvantage in such situations.

10. Although the shock therapy methods are not too securely established universally as entirely desirable procedures in treatment, there can be no doubt as to the stimulation they have given many fields of research including physics, biochemistry, pharmacology, physiology, pathology, psychology, and clinical medicine and psychiatry which have produced a vast number of contributions. It can be said that the whole realm of psychiatry has been vitalized with a renewed interest that will lead to a better understanding of this complex subject and thus to progress in science.

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THE SELECTIVE USE OF ELECTRO-SHOCK THERAPY AS AN ADJUVANT TO PSYCHOTHERAPY*

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would like to preface this paper by the emphatic declaration that I do not approve the indiscriminate use of electro-shock. Without doubt, it carries some risk which varies with the judgment, experience and discretion of the physician. As a therapeutic method, it has provoked repugnance in the minds of many psychiatrists because of its apparent violence; some have referred to it as "sadistic therapy." To this, I reply: "Yes, it appears to be a crude method, but it is the best we have available to us at the present time for the treatment of certain serious mental problems." I am convinced that lives have been saved by this method, lives that would have otherwise terminated in suicide. Moreover, it is a therapeutic method that often enables a patient to carry on the work necessary to his livelihood without the serious interruption of going to an institution. It has spared some people the stigma of having been confined in a mental institution; much as we may deplore the existence of such a stigma, it is a social reality.

We know, too, that the recovery of those patients whose condition requires them to be sent to the mental hospital or sanitarium can often be accelerated through shock-therapy. This is especially true of the melancholias. While less true of the patients with schizoid problems and the severe obsessive compulsive states who are seriously disabled by their torturing symptoms, there are instances in which even these mental disturbances have been favorably influenced by shock-therapy.

I should also like to state most emphatically that electro-shock therapy, like any shock therapy, is woefully incomplete without adequate psychotherapy. In my opinion, a grave injustice is done to any patient who does not receive intensive psychological assistance whenever pos-

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sible. By intensive, I do not mean one or two superficial interviews but a persistent investigation of those factors in the functioning of the personality which led to the mental breakdown. This therapeutic coördination assures a healthier individual, less likely to break down again in a critical situation.

Since it is presumed that practically everyone in this audience has become familiar with the technique of electro-shock therapy, I shall not go into technical detail extensively. The apparatus I used was a Rahm machine with the forceps electrodes; in nearly every instance, the current was for 0.10 second, varying between 70-120 volts. Most of the time, a grand mal convulsion was aimed at; occasionally, petit mal reactions were deliberately induced, but increasing experience seems to point toward the desirability of the major type of seizure to achieve maximum benefit. This is particularly true with regard to the amnesia for the shock experience; the lighter the treatment, the less amnesia, and the less amnesia, the more disturbed the patient seemed to be after the treatment. This disturbance was not only immediate but would often be prolonged for one or more days.

Now, as to the theories regarding the benefits achieved by electroshock therapy, I will mention only two. First, the physiological, and second, the psychological.

Briefly, the physiological interpretations for the improvement obtained by electro-shock are based upon the assumption and evidence that physico-chemical alterations occur. They are:

changes in oxygen-carbon dioxide ratio;2

changes in vascularity of brain areas;8

changes in the cellular structure of the cerebral cortex, as demonstrated by the electro-encephalogram;4

changes in blood pressure, velocity of blood flow, etc.;

changes in chemical contents of the blood.

Since it is relevant to the theme of this paper, I shall dwell more on the psychological aspects of the theories attempting to explain the improvement. There are a number of observers who believe that emotional shock based upon threat (of death) causes the change. Schilder had advocated this point of view and Berkwitz⁵ postulates his technique of repeated daily faradic shock upon this threat factor, among other factors.

When we consider psychological dynamics in mental illness, we are

frequently struck with the patient's inability to do something about a situation. This state may reflect helplessness or inertia. It is my impression that this apathy or inertia is no inconsiderable barrier to the more adequate functioning of the personality and I believe that electro-shock produces the effect of jarring the individual so strenuously that he is summoned to the necessity of facing reality more directly and energetically.

My opinion is that the improvement which occurs is made possible by psycho-physiological alterations affecting feeling tone. By feeling tone, I refer to a quantum of energy tone relating to mood, quality of perception, attitude toward self and attitude towards the world, awareness of capacity to feel the ability to do things, the so-called elan vital. This would derive from those sources within the human organism which are energy producing, e.g., the glandular apparatus, especially the adrenal, the vascular apparatus, etc. This could also be related to the unconscious resistances of the patient to coöperate with those around him, to feel a willingness to help.

The question has often been raised quite naturally: "Does not this seemingly violent assault on the brain cause serious damage to the intellectual functioning of the electro-shocked individual?" It is part of my purpose to demonstrate that not only was there no perceptible impairment of intellectual integrity, beyond the immediate transitory confusional reaction, but that these patients seemed to do better than ever before! I realize this seems extravagant. When we bear in mind, however, the disabling effect of severe emotional disturbance on the intellectual coördination of an individual, we see that this is not so far fetched. The corrosive undermining of the thinking process which constant tension, anxiety, and resentment can cause, is familiar to every experienced student of the psychology of behavior. At this point I would like to stress again that increased assurance for such improved functioning is afforded by adequate psychotherapy to supplement the shock arm of therapeutic management. Such a combination is extraordinarily suitable to office practice because patients make their adjustment to their life situation as they proceed with treatment.

Some Remarks on Dynamics of Therapy

The release of feeling that electro-convulsive therapy enables the patient to achieve is, in my opinion, a factor of importance in moving

the patient along the direction of recovery. Such feeling is perceptible to the trained observer during the initial period of behavior immediately after the seizure, whether of the grand or petit mal type. Particularly significant is the demonstration of hostile feelings: being resistive; gestures of threatening assault; or, being negativistic. Such acts as pushing, punching, slapping at persons surrounding the patient, glaring at them balefully, turning the back on questioning by doctors present are common. As mentioned above, these acts take on added significance when we recall that they tend to be repetitive and that the pattern is characteristic for the individual.

As criteria of progressive improvement, the following observations have been noted:

- 1. Raising of convulsive threshold (but not invariably).
- 2. Decrease in the violence of psychomotor phenomena
- 3. Increased rapidity of return to awareness of surroundings immediately following the convulsion
- 4. Lessening of memory impairment following convulsion in the later stage of treatment, compared to the early period
- 5. Usual clinical indications of improvement; being more cheerful; gain in weight; sleeping better; willingness to coöperate at home; more outgoing in behavior generally with a corresponding diminution of inertia; being more assertive to the extreme point of acting aggressively at times.⁶

It is of great interest to note the varying flexibility of patients in this release of feeling. In dealing with rigid personality structures where lack of spontaneous affective expression, impassivity of facial expression, and silence are pronounced, the array of postconvulsive psychomotor activity is relatively violent. This violence is in striking contrast to the daily behavior of the patient, particularly so in cases of depression. Then, as the spontaneity of feeling becomes more evident in the course of improvement, there is a corresponding decline in this postconvulsive agitation. Such an inverse ratio in behavior is, of course, not mathematically exact. But it appears to furnish an index of the degree of restraint and suppression which the sick person exercises over the impulses that he fears to express.

There are a number of observations occurring during electro-shock therapy which are interesting. Let us turn our attention to the memory impairment or amnesia. There is fragmentation of memory with com-

plete loss for recent events. The retention of memory follows an ontogenetic pattern of memory development:

- 1. Knowledge of personal name
- 2. Name of closest relatives: husband or father or mother or wife or children
- 3. Home address—but even here they may give a former home address instead of the present one, especially if the present one possesses some painful association, illustrating the mechanism of repression in amnesic states
- 4. Place of work or affiliation connected with work outside of home
- 5. The doctor's face will appear familiar but there may be prolonged difficulty in recalling his name. This is of peculiar interest since the patient will often remember the name of an assistant physician or nurse sooner than the physician administering the treatment. Here, again, we see the factor of repression in amnesia, to shut out painful impressions and associations
- 6. They recall the date, day, and month last, and with this recollection a flood of detail rushes back into conscious intellectual awareness. For example, they can then recall events which preceded the treatment during the morning or afternoon.

The order of memory retention is better understood when we point out that No. 2 and No. 6, for example, do not appear together immediately after the treatment. This would suggest that certain associational patterns in the areas of the cerebral cortex which subserve memory function are disturbed in the order of their temporal development. That is to say, the most recently developed memory for experiences is most vulnerable to disruption by electro-shock. This phenomenon, we recognize, is in accordance with Hughling Jackson's concept of dissolution of brain functioning occurring in the order of ontogenetic growth from primitive to more recently developed cerebral structures.

Although there are a number of points of psycho-physiological interest that lend themselves to extended discussion, mention will only be briefly made insofar as they are relevant to the subject of this paper.

First, is the general observation that each individual repeats a psychomotor pattern which tends to be characteristic for the individual. For example, one patient will manifest arm thrashing movements immediately after the cessation of the major fit in the first few treatments. Another will repeat leg thrashing movements, like a running pattern.

A number of patients, more likely those suffering from depression, will clench their jaws strenuously, resisting every attempt to remove the mouth gag. One patient used to reach out, in the twilight period of confused disorientation of semi-consciousness, and force the operator's hand to return the gag to his mouth. (The suggestive implications about oral drive are obvious). Many times one will observe sucking movements persisting after removal of the mouth gag, but I have never been able to elicit a genuine forced grasping reflex.

As they emerge into this twilight zone of semi-stupor from deep stupor, a pronounced startle pattern can be seen in a number of people when anyone approaches the treatment couch, or if someone speaks above a whisper. This resembles the wild primitive violent reflex of running amok, for the patient will shriek and shrink in terror or make belligerent gestures toward the approaching person. Another patient will begin to sing a bit of a child's song; this occurs seldom as most of the patients are mute and groan a bit and then seem to fall asleep. This sleep seems to be the most favorable type of after-convulsive reaction, for they are much more tranquil afterward, than if they show agitation and alarm about their disorientation during the semi-stupor.

Now, it may be very properly asked, "What is the meaning of this shock treatment for the patient?" And here we resort to material given by patients themselves. One said, "What have you done to me? I feel as though I'm reborn!" I have the impression that some patients react to shock treatment as a form of physical punishment, just as they may react to psychotherapeutic sessions as scoldings. Although the opinion has been expressed by some observers that patients do not seem to mind electro-shock treatment, I must disagree. While not comparable to the terror which metrazol held for patients, it has been my experience that electro-shock did frighten them. The level at which this dread was stored was unconscious usually, although some patients have told me that they consciously were afraid. They could not tell why, especially those who had major fits, but they sometimes would balk at taking a treatment. After a petit mal, particularly the brief and light variety, patients seemed very resentful and uncomfortable.

In my opinion, the shock treatment affects the psyche of the patient as a profound threat to his very existence. It reaches down to something primitive—we can call it the instinct for self preservation—or ego instincts—or what you will—in the human organism. Certainly, it is a

fact that they regard the loss of consciousness resulting from the treatment with dread; they feel that they must completely surrender themselves to the mercy of others as one undergoing general anesthesia. The same doubt as to whether they will emerge alive is operative in shock therapy. Significantly, a common reaction is to find early disappearance of suicidal impulses among the psycho-pathologic phenomena of the patient's mental disorder. One may speak of a reintegration of ego structure made possible by a violent shock to the personality.

With regard to the psychotherapy: should it be done by the same person who administers the shock? There are advantages and disadvantages in having the same doctor for both. One advantage is the matter of convenience; another is the opportunity to study every phase of the patient's behavior. It would seem of optimum benefit if the psychiatrist who is to administer psychotherapy could be present to assist the physician administering the electro-shock. In my experience, being the psychiatrist in addition to the one who also administers the electro-shock has not proven a serious obstacle in continued psychotherapy. Nevertheless, it is quite conceivable that a patient may be repressing resentment towards the electro-shock therapist to a degree which would make a desirable transference very difficult to attain for continued psychotherapy.

SUMMARY

There are instances in psychotherapy where the resistances of the patient are of such a character as to make an exclusively psychological approach unfeasible. In such cases, the supplementary value of electroshock is to be borne in mind as a procedure which affects the rigidity of the psycho-pathological personality structure so that the patient is rendered more accessible to psychotherapy. The benefit derived from electro-shock seems to stem from psycho-physiological alterations which stimulate the individual's will to live and reduces the withdrawal tendency.

Finally, it may be said that whatever doubt may exist about the dynamics of improvement, there can be no doubt of the empirical fact that electro-shock therapy is an important contribution to the art and science of mental healing.

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CERTAIN ABNORMALITIES OF OCULAR MOVEMENTS. THEIR IMPORTANCE IN GENERAL AND NEUROLOGIC DIAGNOSIS*

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added to our knowledge of ocular movements and ocular fixations. Since such observations have been described individually in different journals, redescription of them here may be permissible. Certain of them are important in regard to the cerebral integration of ocular movements—a subject which has been ably discussed by Holmes.¹ Part I of this paper is designed to review essential features which point to supranuclear lesions as the cause of abnormalities of conjugate movements and to redescribe relatively recent contributions in this field. The presentation is necessarily incomplete and concerns principles of diagnosis rather than precise anatomy. Part II contains a description of phenomena which arise through misdirection of regenerated fibers in the third nerve. These phenomena have been described previously by Bender,² Ford and Woodhall,³ Bender and Fulton⁴ and by Bielschowsky.⁵ Their importance in the diagnosis of congenital aneurysms of the circle of Willis has been noted by Walsh and King.⁶

PART I. (A) THE SUPRANUCLEAR MECHANISMS WHICH CONTROL OCULAR MOVEMENTS

The mechanisms which initiate and control conjugate movements of the eyes are described below under the following headings: (1) Frontal lobes and volitional control of conjugate ocular movements; (2) Occipital lobes and optic fixation reflexes; (3) Labyrinthine reflexes (a) semicircular canal reflexes, (b) otolith reflexes; (4) Tonic neck reflexes.

Frontal Lobes and Volitional Control of Conjugate Ocular Movements. Volitional movements of the eyes originate in cortical centers

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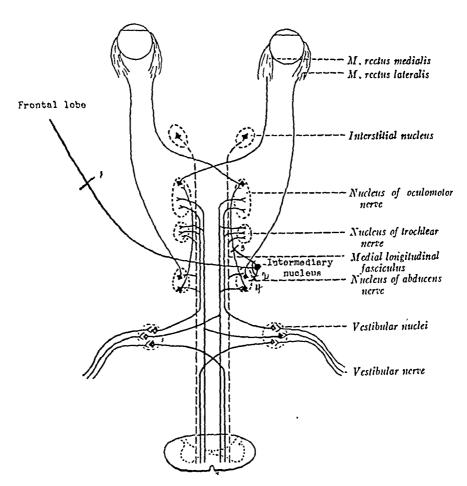


Fig. 1-Diagram showing the connections of the medial longitudinal fasciculus. (Modified from Villiger.) Further modified from Ranson to show results of lesions interfering with supranuclear pathway.

Lesion at 1 (in the hemisphere) results in conjugate deviation of the eyes to the side of the lesion.

Lesion at 2 results in conjugate deviation of the eyes to the side opposite the lesion.

Lesion at 3 results in anterior internuclear paralysis. Lesion at 4 results in posterior internuclear paralysis.

termed "oculogyric centers" situated in the frontal lobe of each side, the area being frequently designated as area 8 (Brodmann). Electrical stimulation of this area on either side produces conjugate movement of the eyes (and usually the head) to the opposite side. If the lower part of the area of one side is stimulated there is upturning of the eyes in addition to the lateral movement, and if the upper portion is stimulated there is additional downturning added to the lateral movement. Ablations produce opposite results.

From these frontal cortical areas projection fibers enter the anterior

part of the internal capsule and reach the cerebral peduncles where they become detached from the corticospinal tract in small bundles at successive levels in the brain stem. They move dorsally to lie close to the medial lemniscus in the tegmentum. Then they undergo partial decussation and reach the intermediary supranuclear nucleus principally of the opposite side. It is from this level that impulses are mediated to the medial longitudinal fasciculus which is shown diagrammatically in Figure 1. Actually the position and course of the projection pathways from the frontal oculogyric centers has been postulated by Déjérine and never entirely confirmed. Further, it is fairly generally agreed that intermediary supranuclear nuclei exist but Collier amongst others does not believe such nuclei are necessarily present.

Occipital Lobes and Optic Fixation Reflexes. When it was found that stimulation of the frontal lobe cortex produced contralateral conjugate movement of the eyes it was observed also that stimulation of the region surrounding the striate area likewise produced contralateral ocular movements. If, however, the frontal lobe and the opposite occipital lobe were stimulated at the same time the movement of the eyes always corresponded to the frontal lobe stimulation. Thus stimuli from the frontal lobes, the volitional centers, are stronger than stimuli from the occipital lobes. It is obvious that optic fixation centers must exist in the occipital lobes.

In the optic fixation reflex the afferent pathway is via the optic nerves and optic pathways. The corticofugal pathway is from the occipital cortex (mainly areas 18 and 19), down the internal sagittal stratum to the posterior limb of the internal capsule, round the inferior aspect of the optic thalamus to the superior colliculus and from thence to the brain stem. This pathway has been described by Kronfeld. It is remarked in passing that the optic fixation reflexes utilize cerebral cortex whereas vestibular reflexes apparently do not reach that level.

Labyrinthine Reflexes. The eyes may be conjugately deviated through the influence of sound as well as other sensations, but here we are concerned only with reflexes which are essentially vestibular in origin. These were analyzed by Breuer as long ago as 1875 with such exactitude that, as de Kleijns has remarked, little has been added. Clinical observations are set forth below and they conform to the results of experiments performed by Breuer and confirmed by de Kleijn among others. Breuer divided vestibular reflexes into two principal groups

which are now described in brief.

- (a) Semicircular canal reflexes are stato-kinetic, that is they produce a physiologic response to movement or to acceleration of movement. The stimuli probably arise through pressure of endolymph on the sensory end organs in the ampullae of the semicircular canals. Such reflexes account for brief contractions of skeletal muscles. In normal individuals this is exemplified in the occurrence of vestibular nystagmus which is essentially a jerky nystagmus. Semicircular canal reflexes have for long been known to be responsible for ocular fixations during movements of the head, but this knowledge has rested upon the results of experimental work until relatively recently. Since it has become known that section of the vestibular nerve or nerves is an effective method of treating Meniérè's disease evidence of pure vestibular dysfunction has been recognized clinically. Levin⁹ described a unique case in which the vestibular nerves were selectively involved and in which the resultant symptoms were identical with those observed after surgical section of both vestibular nerves.
 - (b) Otolith reflexes are static reflexes and are responsible for tonic reactions. Magnus has shown that changes in the position of the head in its relation to space produces postural reactions which consist of assumed positions of the limbs and tonic deviations and rotations of the eyes. These reflexes arise in the labyrinth since they persist after the three upper cervical dorsal nerve roots on each side have been sectioned (de Kleijn), and they disappear after bilateral labyrinthectomy. Otolith reflexes seemingly arise as the result of weight of the otoliths and gravity. Consequently, turning the head into a lateral position does not call forth an otolith response because the position of the head is not altered in the field of gravity. When the head is flexed the eyes are deviated upward and when the head is extended the eyes are deviated downward as a result of otolith reflexes. When the head is inclined to one or other shoulder the eyes are rotated on the visual axis in the opposite direction to compensate for the altered position of the head. This last named evidence of otolith function is of real importance in the diagnoses of palsies of vertically acting muscles.

McNally and Tait 10 believe that the sacculus otoliths have nothing

to do with tonic reflexes.

Tonic Neck Reflexes. These reflexes are of relatively slight significance in man, but they are most important in animals particularly those in which the eyes are placed laterally in the head.

Tonic neck reflexes arise from proprioceptive nerve endings in the muscles of the neck as has been proven by their disappearance after section of the cervical nerve roots on each side. That tonic neck reflexes occur in the absence of labyrinthine reflexes is proven by their persistence after section of the vestibular nerves as was present in Levin's case, and as has been proven experimentally when they persist after destruction of the labyrinths. Tonic neck reflexes depend upon the position of the head in relation to the trunk. If the head is immobilized and the trunk is then moved, or if the labyrinths are destroyed and the head is moved, the tonic neck reflexes become apparent. In the latter instance, when the head is flexed, the eyes move upward and if the head is extended the eyes move downward, and if the head is inclined in one plane the eyes move in the opposite plane. From this it is apparent that tonic reflexes are supplementary to otolith reflexes and vice versa.

Labyrinthine and optic righting reflexes do not require consideration here.

PART I. (B) SUPRANUCLEAR LESIONS AND THEIR EFFECTS UPON OCULAR MOVEMENTS

We are now in position to analyze the effects of certain supranuclear lesions from the standpoint of their influence upon ocular movements. Because of time limitation lesions influencing convergence and divergence are not considered.

It has already been remarked that experimenters abolish the function of one mechanism in order to study the function of another. Thus in order to study tonic neck reflexes it is necessary to abolish labyrinthine (otolith) reflexes and conversely if otolith reflexes are to be studied the tonic neck reflexes must be abolished. In the clinical study of supranuclear lesions, particularly when they are in the hemisphere, advantage is taken of the fact that suspension of volitional control enhances the optic fixation reflexes. If the eyes cannot be moved voluntarily into a desired position it is proven that the lesion is supranuclear if such movement can be obtained through the effect of some other mechanism which takes part in the movement but cannot be identified as participating in the normal individual. Since we are here concerned with abnormalities of ocular movements the subject of supranuclear lesions is considered from the standpoint of position of the eyes.

I. LOSS OF VOLITIONAL CONTROL WITH CONJUGATE DEVIATION OF EYES TO THE SIDE OF THE LESION

Conjugate deviation of the eyes to the side of the lesion and inability to move them to the opposite side is present in a majority of cases of vascular accident when the lesion is situated in the hemisphere. To rationalize this statement it is only necessary to recall that electrical stimulation accounts for contralateral conjugate movements of the eyes, and that ablation accounts for conjugate deviation of the eyes to the side of the lesion.

With James I. Moore, I have studied more than fifty cases of cerebral hemorrhage in which there was a unilateral lesion. In such cases the lateral deviation of the eyes is pronounced. The deviated position is 'maintained in many instances for only a few hours and has always, in our experience, disappeared within a week or thereabouts. The head is usually deviated in the same direction as the eyes. In such patients, during the time that deviation of the eyes is present, there is loss of volitional control of the eye movements. Optic fixation reflexes are present and active when the patient is in contact, and in some cases the optic fixation reflexes are seemingly exaggerated. Thus they may be utilized in moving the eyes into positions otherwise unobtainable, and such movement is proof of the supranuclear origin of the lesion. Bilateral hemispheric lesions may account for complete inability to move the eyes conjugately or separately in any direction through voluntary effort. In such cases the defect is usually more or less permanent.

Various maneuvers are undertaken to obtain movement of the eyes into otherwise unobtainable positions insofar as the patient's efforts are concerned. Since in actual practice these maneuvers are undertaken to bring either optic fixation reflexes or labyrinthine reflexes into active functioning the various procedures are now outlined.

If a patient exhibits pronounced deviation of the eyes and head to the right there is inability to voluntarily move the eyes to the left. The following maneuvers may suffice to obtain the voluntarily impossible movement of the eyes.

1. The patient is asked to fix the light on a test object which is moved slowly in front of the eyes from right to left. In some instances the eyes will follow the light. This is called the following movement.

2. With the patient fixing the light, the head is grasped in the

examiner's hand and is slowly rotated in the appropriate direction. The eyes may move into the desired field.

If volitional control of the eye movements is not entirely lost but is weakened the resulting relative efficiency of the optic fixation reflexes may account for inability to move the eyes until blinking interrupts the fixation reflex.

3. In some instances where voluntary movement of the eyes is impossible, if a light is held in the seemingly unobtainable field, the eyes are immediately turned toward the light. Bielschowsky⁵ considered this to be an optic fixation reflex.

From consideration of the tests mentioned above it becomes apparent that loss of volitional control in some instances enhances the optic fixation reflexes and may make them relatively excessive. However, it is not always possible to use the optic fixation reflexes since the patient may be unconscious; he may refuse to coöperate although conscious, or the optic fixation reflexes may not serve to obtain the desired deviation of the eyes. In such instances other maneuvers may be employed and in these the vestibular reflexes are utilized.

- 4. The patient's head is grasped by the examiner and is rapidly rotated when it may be noticed that the eyes deviate momentarily into the position desired by the examiner. This reflex movement is thought to be due to reflexes arising in the semicircular canals for it is of brief duration and is entirely different to that elicited by slow rotation of the head with the eyes fixing as has been mentioned above (2).
- 5. The caloric test may be used. If, in the example being considered, namely when the eyes are deviated to the right, the left ear is syringed with cold water the eyes move conjugately to the left. This is providing the paralysis of ocular movement is supranuclear in origin and originates from a lesion in the hemisphere, and further providing the vestibular pathways are intact.

The caloric test has certain advantages over rotation tests which are not considered in this paper. One of the most obvious advantages is that the caloric test can be performed on patients who cannot be placed in a rotating chair.

II. LOSS OF OPTIC FIXATION REFLEXES WITH RETENTION OF VOLITIONAL CONTROL

Lesions which interfere with functioning of the posterior oculogyric

apparatus may abolish the capacity for optic fixation without interfering with visual acuity or with the visual fields. Since, however, such lesions are likely to interfere with the striate cortex and (or) with the optic radiations, loss of optic fixation reflexes is rarely observed as an isolated symptom. Abnormal functioning of the posterior oculogyric apparatus is seen much less often than involvement of the anterior oculogyric apparatus.

The symptomatology of lesions affecting the posterior oculogyric apparatus has been well illustrated in a case described by Holmes and Horrax. Their patient, a soldier suffering from the effects of a wound involving the optic pathways, exhibited loss of a quadrant of the lower visual field in each eye. Central visual acuity was normal and there was no evidence of paralysis of the extraocular muscles. The following features were described: (1) There was difficulty in fixation. He could maintain fixation on an object when he found it but there was great difficulty in locating it. (2) Accommodation-convergence was affected. If an object were brought close to his eyes he could not converge his eyes on it, but if the object were his own finger convergence was performed normally. (3) When objects were shoved close to his eyes he did not blink unless the object happened to be his own hand when blinking was prompt. (4) Visual word memory was altered. He was unable to describe the manner in which he found his way about in trenches with which he was familiar. (5) While he could recognize movements of objects he did not know whether they were being moved to or from him. (6) He could read only with difficulty and could not find the start of the following line. (7) Stereoscopic vision was lost. (8) Volitional movements of the eyes were not influenced. With Frank R. Ford, I have described a somewhat similar case in which there was loss of the optic fixation reflexes as a result of nitrous oxide anesthesia.

At this time a generalization may be made regarding the differentiation of lesions involving the anterior and posterior oculogyric mechanisms. Lesions interrupting the anterior apparatus produce relative increase in the optic fixation reflexes and conjugate deviations to the side of the lesion when it is destructive and in the hemisphere, and to the opposite side when it is irritative. Lesions involving the posterior oculo-opposite side when it is irritative. Lesions involving the posterior oculo-opposite apparatus, often complicated by lowering of visual acuity and gyric apparatus, result in inability to properly fixate objects with the eyes field defects, result in inability to properly fixate objects with the eyes but not in interference with volitional movements of the eyes.

III. LOSS OF VOLITIONAL CONTROL WITH DEVIATION OF THE EYES AWAY FROM THE SIDE OF THE LESION

As has already been described when the lesion is in the hemisphere the eyes are directed toward the side of the lesion and there may be inability to move them to the opposite side. Since, however, the projection fibers from the frontal lobe cortex cross in the midbrain for the most part, a lesion in the midbrain accounts for deviation of the eyes away from the side of the lesion and for paralysis of volitional movement of the eyes to the side of the lesion. There are other important differences between lesions at this level and hemispheric lesions and I cannot do better for description than include Bielschowsky's table.⁵

LATERAL CONJUGATE DEVIATIONS OF THE EYES (BIELSCHOWSKY)

Lesions in the Hemisphere

- 1. In the first stage regular and of considerable magnitude.
- 2. Deviation usually of short duration.
- 3. Deviation toward the side of the lesion.
- Deviation frequently a sign of stimulation.
- Head turned (as a regular symptom) in the same direction as the deviation of the eyes.
- Associated paralysis of muscles for contralateral movements, usually slight and transient.
- 7. Invariably symmetrical functional disturbances of associated muscles.
- Paralysis of extremities and of facial nerve collateral with the associated eye muscle paralysis.
- In lesions of both hemispheres all eye movements (including the vertical) restricted or impossible.

Pontine Lesions

- Relatively rare and as a rule of small magnitude.
- 2. Deviation, if present, permanent.
- 3. Deviation toward the opposite side.
- Deviation usually a paralytic symptom, only rarely a sign of stimulation.
- 5. Abnormal position of the head not typical symptom if present.
- Associated paralysis in the direction of the lesion always severe and permanent.
- Frequently asymmetrical paralysis of associated muscles in consequence of extension of the supranuclear lesions to nucleus or nuclei.
- 8. Paralysis of extremities, if present, opposite to the side of the eye muscle paralysis. Paralysis of the facial nerve, if present, usually collateral with the eye muscle paralysis.
- In pontine lesions of both sides paralysis of side to side movement without paralysis of vertical movements.

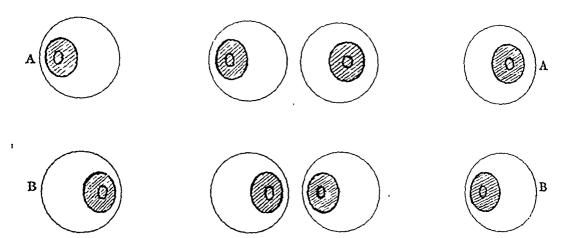


Fig. 2 (1)—A. Conjugate deviation to the side of the lesion: lesion in hemisphere: paralysis volitional movement to left. B. Eyes may be moved to left: (1) by utilizing optic fixation reflexes; (2) by impulses from semicircular canals (quick rotation of head); (3) by caloric stimulation (cold water in left ear); (4) by proper rotation.

Fig. 2 (2)—A. Conjugate deviation away from side of lesion (lesion in pons): paralysis volitional movement to the right: convergence ability retained. B. Eyes may be moved to right by caloric stimulation right ear and by proper rotation tests.

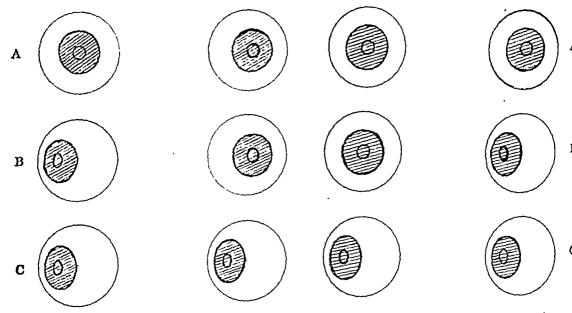


Fig. 2 (3)—Anterior internuclear paralysis. A. Eyes straight: convergence ability retained; B. Eyes right: left eye fails to turn to right; C. Left eye turns to right after caloric stimulation (cold water right ear).

Fig. 2 (4)—Posterior internuclear paralysis. A. Eyes straight; B. Eyes right: left eye turns to right but right eye fails to do so; C. Right eye turns to right after caloric stimulation or rotation.

Fig. 2. Diagrams illustrating paralyses of lateral conjugate movements (lesions on right).



Fig 3—T Z. Patient suffered from glioma of the pons. There was paralysis of the right 6th, 7th and 8th nerves, paralysis of conjugate movement to the right. The eyes could be converged but caloric stimulation of the right vestibule failed to produce adduction of the left eye. Doubtless the vestibular tract on the right had been destroyed.

We may now consider abnormalities of lateral conjugate movements of the eyes as the result of lesions in the brain stem. If there is a unilateral supranuclear lesion which affects conjugate ocular movements it may involve: (1) the supranuclear intermediary center in the region of the sixth nerve nucleus. If the lesion is on the right there is slight deviation of the eyes to the left and they cannot through volition be moved to the right. The power of convergence is retained. If the right ear is syringed with cold water the eyes usually move freely to the right. (2) The lesion may involve not only the supranuclear center of one side but may invade the sixth nerve nucleus and nuclei of other cranial nerves usually on the same side. Figure 3 shows such a lesion. The patient suffered from a glioma of the pons. There was paralysis of the right sixth, seventh and eighth nerves. The eyes could be converged. Caloric stimulation (cold water into the right ear) failed to produce adduction of the left eye hence the vestibulo-ocular pathway was also

interrupted. (3) The lesion may be situated in such a position that it interferes with impulses passing to the opposite internal rectus muscle. Such a lesion usually is in the medial longitudinal fasciculus. This comprises an anterior internuclear paralysis. (4) The lesion may be situated in a position to interfere with impulses reaching the sixth nerve nucleus while not interrupting impulses reaching the contralateral internal rectus muscle. This comprises a posterior internuclear paralysis. (5) There may be bilateral lesions which involve both supranuclear centers in the pons. In this instance there is inability to move the eyes voluntarily either to the right or left, but vertical movements and the ability to converge are retained. In such instances caloric stimulation serves usually to deviate the eyes in the desired direction. I have observed such a bilateral paralysis of supranuclear type in a child suffering from glioma of the pons. Bilateral anterior internuclear paralysis has been described by Spiller. His patient could not adduct either eye during attempts at lateral conjugate movements but was able to converge the eyes normally. Probably bilateral posterior internuclear paralysis has been described but if so I have overlooked the description.

It has been said that as a result of hemianopsia there may be conjugate deviation of the eyes. Although deviation of the head undoubtedly is observed frequently in association with hemianopsia in order to increase the size of the visual field I have not observed conjugate deviation of the eyes in the absence of deviation of the head in such cases. The patient with hemianopsia may exhibit awkwardness in looking toward the blind field but this should not usually be confused with paralysis or paresis of conjugate movement.

IV. LOSS OF ABILITY TO VOLUNTARILY ELEVATE AND DEPRESS THE EYES

Up to this point only abnormalities of lateral conjugate movements of the eyes have been mentioned. Of equal importance, but of less frequent occurrence in my experience, is inability to voluntarily elevate and depress the eyes. Such ocular paralyses arise as the result of supranuclear lesions.

The mechanisms through which volitional upward and downward movements of the eyes are obtained are not so readily visualized as those for lateral movements. Holmes¹¹ has predicated the existence of intermediary centers in the midbrain at about the level of the superior colliculus. That for upward movements, he states, is anterior, and pro-

gressing downward there is a center for downward movement and one for convergence.

Inability to voluntarily direct the eyes upward or downward is commonly described as Parinaud's syndrome. The diagnosis of supranuclear lesions for such a disability requires mention of further maneuvers or tests not as yet mentioned.

- 6. With the eyes fixing, the patient's head is slowly flexed when the eyes may turn upward, or if there is inability to look downward extension of the head may account for downturning of the eyes.
- 7. Bell's phenomenon may be exhibited as proof of the supranuclear origin of the paralysis. The patient is asked to close the eyelids while the lids are held open by the examiner. If Bell's phenomenon is present the eyes are turned upward.
- 8. If caloric stimulation is applied while the patient holds the head flexed as far as possible, or preferably in our experience if the head is tilted to one or the other shoulder, tonic upward deviation of the eyes may be obtained. A similar result is obtained when rotation is performed.

The presence of Parinaud's syndrome suggests a lesion in the region of the quadrigeminal plate, often a pineal tumor. We have observed the development of a typical case in a young girl. The first abnormality noted was wide dilatation of the pupils which failed to react to light. Then there was inability to voluntarily look upward, and finally there was inability to look downward as well. Parinaud's syndrome may be observed in association with ptosis and small actively reacting pupils as we have observed. In some instances the syndrome is transient as has been observed by Dr. Arnold Knapp and by the present writer. In such cases there may be an associated unilateral or bilateral proptosis in rare instances.

While on the subject of paralysis of upward and downward movement of the eyes as caused by supranuclear lesions mention may be made of a unique case which has been described by Dr. Ford and the writer. The clinical studies on this case followed the pattern of studies made by experimenters on animals. This case appears to stand alone as clinical proof of the function of the otolith organs in man.

Case 1. Congenital double athetosis associated with congenital paralysis of upward and downward movements of the eyes in a boy 13 years of age; elevation and depression of eyes obtained by active and passive movements of the head.



Case 1—Volitional movements of the eyes. A shows full range of movement to the right, and B, full range of movement to the left.



Case 1—Deviations due to movements of the head. A shows deviation of the eyes downward when the head is passively extended, and B, deviation upward when the head is flexed.



Case I—Reactions on the tilting table. A shows upward deviation of the eyes due to bringing the patient from a horizontal to an upright position. B shows downward deviation of the eyes due to rotating the patient from an upright position backward to a horizontal position.

Fig. 4—(Case 1). Congenital double athetosis associated with congenital paralysis of upward and downward movements of the eyes in a boy 13 years of age; elevation and depression of eyes in the orbits obtained by active and passive movements of the head. (Ford and Walsh.)

- L. S. was examined on June 15, 1939. Neurologic examination revealed the usual signs of double athetosis which was known to be stationary and had been noted in early childhood. It had never been possible for the child to make satisfactory progress in learning to read despite the fact that his intelligence seemed to be normal. His teachers stated that the difficulty seemed to lie in his inability to move the eyes properly. Examination of the eyes yielded the following observations:
- 1. Vision and visual fields were normal. The pupillary reactions were brisk. The optic fundi were normal.
- 2. Voluntary movements of the eyes to the right and left were normal. He could follow a moving object to either side.
- 3. Voluntary movements of the eyes downward below the horizontal were absent. When fixation was prevented by closing the eyes there were still no downward movements.
- 4. Voluntary movement of the eyes upward was difficult and was limited to less than 10 degrees.
 - 5. Convergence was entirely absent.
- 6. It was impossible for the patient to follow a test object moving slowly in the vertical plane. This test was made repeatedly. The revolving drum failed to elicit any reaction when it was revolved about a horizontal axis.
- 7. When the patient's head was extended actively or passively, compensatory deviation of the eyes downward occurred. By this means the eyes might be deviated to the limit of their normal excursion. In the same manner flexion of the head caused upward deviation of the eyes. These reactions were secured just as easily when the eyes were closed as when they were open and by slow movements of the head as well as by rapid movements. They were constant and never varied in the slightest degree.
- 8. The patient was placed on a tilting table in such a manner that no movement of the neck could occur. When he was rotated from an upright position backward the eyes deviated downward just as when his head was extended on his body. When he was rotated from a horizontal to a vertical position his eyes deviated upward just as when his head was flexed on his body. It was clear that it was the change in the position of the head in space and not any movement of the head on the body that caused the deviation of the eyes. The ocular deviations were well sustained.

- 9. The patient had learned an interesting trick by which he could deviate his eyes downward. When asked to look at an object in his lap he would flex his head and the upper part of his trunk as strongly as possible. During this movement his eyes were, of course, rotated upward in the orbits, but by extreme flexion of the spine he could finally bring them to bear on the test object, for the range of movement of his head was greater than that of his eyes. At this point he would bring his head into the upright position and his eyes would remain fixed on the test object in the position of downward deviation. The examiner could reproduce this reaction by making passive movements of the patient's head. It was also possible to fix the patient's eyes on a test object above his head by making extreme extension of the head and then bringing it into an upright position. The patient failed to discover the latter maneuver until it was shown him.
 - 10. Bell's phenomenon was present.

In the case described above it seemed that otolith reflexes were responsible for the tonic deviations of the eyes for the following reasons: (1) There was loss of optic fixation reflexes in the vertical plane as demonstrated by absence of optikokinetic nystagmus with the axis of the drum placed horizontally. Furthermore optic fixation reflexes could not have produced the tonic deviations because the position of the eyes changed when fixation was abolished by closure of the lids. (2) The possibility of semicircular canal reflexes being responsible was eliminated by the tonic nature of the ocular deviations. Semicircular canal reflexes are of brief duration. (3) Tonic neck reflexes were ruled out by observation of upward and downward deviation of the eyes when the patient was placed on the tilting table. (4) The reactions were in the field of action of the otolith organs, that is they were produced by alterations of the position of the head in space, and were sustained.

The second case which is described in summary illustrates the result of section of both vestibular nerves. It is to my knowledge the first such case to have been described (Ford and Walsh¹³).

Case 2. Man 43 years old developed paroxysms of vertigo with mild reduction of hearing and some tinnitus. Operative section of the vestibular components of both eighth nerves with complete relief of original symptoms. Postoperative development of unsteadiness on turning head and uncertainty when crossing streets. Loss of ocular fixation dur-

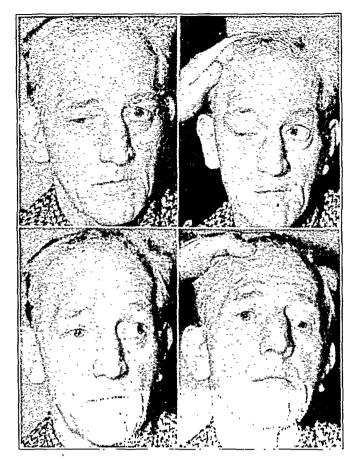


Fig. 5—Regeneration with misdirection of fibers. When adduction or downward movement was attempted the lid became elevated. Case of saccular aneurysm of right internal carotid artery, in a man aged 58, treated by partial ligation of artery in neck and a month later by intracranial ligation; degeneration of third nerve producing abnormal movements of lid associated with ocular movements; partial recovery from internal ophthalmoplegia; abnormal pupillary movements. (Walsh and King⁶)

ing movements of the head. No change in hearing, but complete loss of all vestibular reflexes.

J. B., 43 years old, developed paroxysms of vertigo often accompanied by vomiting which sometimes lasted a day or more. There was slight tinnitus aurium on either side and mild reduction of hearing in both ears, more pronounced on the left. The vestibular reflexes were normal. Neurological and medical examination revealed nothing of importance except for mild hypertension. A diagnosis of paroxysmal aural vertigo or Meniérè's disease was made. The patient was treated

by various conservative methods without result.

Craniotomy was performed and the vestibular components of both eighth nerves were severed. This put a stop to the paroxysms of vertigo and resulted in complete loss of all vestibular reactions on turning and irrigations of the ears. The audiometer chart showed no change in hearing following the operation.

After operation it became apparent that a new series of symptoms had developed. Objects seemed to move before his eyes unless his head was kept perfectly still. Walking caused objects to "jump" before his eyes to some extent, but this did not interfere with his gait. He was unsteady because he had to turn his head to look for approaching cars. Consequently he had become accustomed to hold his head very stiffly and walk in straight lines looking directly before him. He was unsteady in the dark. These symptoms were unchanged after 14 months. Vestibular stimulation either in the form of caloric stimulation or rotations failed to produce nystagmus. The optic fixation reflexes were responsible for normal optikokinetic nystagmus.

Summary Part 1: The abnormalities of conjugate ocular movements and of optic fixations have been described from the standpoint of supranuclear lesions situated at different levels. The function of the semicircular canals in controlling optic fixations during movements of the head has been described from a clinical standpoint, as has a case illustrating the normal function of the otolith. Emphasis has been given to the few procedures which point to abnormalities of ocular movements being caused by supranuclear lesions.

PART II. MISDIRECTION OF REGENERATED FIBERS IN THE THIRD NERVE

Misdirection of fibers during regeneration results in some instances in anomalous movements of the upper lid, abnormalities of movements of the globe, and in pupillary anomalies. These phenomena may properly be attributed to misdirection as has been described by Bielschowsky, Bender, Bender and Fulton and Ford and Woodhall. Walsh and King remarked upon the importance of the misdirection phenomena in the diagnosis of congenital aneurysms of the circle of Willis.

During regeneration, as has been pointed out by Cajal and others, there is multiplication of nerve fibers. These fibers become misdirected or mixed in their distribution. Thus fibers designed to reach the internal rectus muscle may reach the superior rectus while others intended for

the inferior rectus may reach the levator palpebrae and so on. This hypothesis is easier to prove in the instance of regeneration in the third nerve than it is in the seventh where it accounts for mass facial movements.

The following observations may be made regarding the lids and ocular movements in a case of misdirection after recovery from third nerve paralysis. (1) The patient can adduct the eye normally. The internal rectus muscle is not opposed by any muscle innervated by the third nerve, hence the normal internal movement. (2) The eyeball cannot be elevated or lowered because the superior and inferior rectus muscles oppose each other actively. That there is not a paralysis of either of these muscles has been shown experimentally by Bender and Fulton.4 If they sectioned the superior rectus muscle the eye could be lowered. (3) When the eye is adducted the upper lid is elevated. The levator palpebrae is unopposed by any muscle innervated by the third nerve hence the outflow of impulses causes it to elevate sharply when the eye is adducted either in convergence or in lateral movement. (4) The upper lid is lowered when the eye is abducted. This is in conformity with Sherrington's dictum regarding reciprocal innervation of the extraocular muscles.

The following observations have been made by Ford, Walsh and King¹⁴ regarding pupillary movements after third nerve regeneration.
(1) The pupil may be large and fail to react to light on convergence.
(2) The pupil may be either larger (usual) or smaller (rare) than its fellow and may fail to react on direct light stimulation but reacts during convergence and any movement during which the eye is adducted. (3)

convergence and any movement during which the eye is adducted. (3) The pupil may react sluggishly to light and more actively during convergence or any movement in which the eye is adducted. (4) The pupil in the affected eye often dilates during abduction of that eye. This again exemplifies the validity of Sherrington's observations regarding reciprocal innervation.

In commenting upon the pupillary phenomena which are associated with regeneration of the third nerve it has been remarked that one of the pupillary anomalies resembles the Argyll Robertson pupil. Furthermore, it is of particular interest that regenerating somatic motor nerve fibers may establish effective synapses with post-ganglionic neurons of the autonomic system.

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THE MANAGEMENT OF THE PATIENT WHO HAS RECOVERED FROM ACUTE CORONARY OCCLUSION*

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result from various causes. The most common pathological processes responsible are atherosclerosis and thrombosis. This discussion will be confined to a consideration of acute obstruction followed by infarction of the myocardium due to such lesions. The anatomical changes which subsequently take place in the heart muscle are directly related to the course of the illness and, consequently, to therapeutic procedure. Reference will be made to them in appropriate places.

When may it properly be said that a patient has recovered from the acute phase of an attack? The uncertain period following cardiac infarction is during the first two weeks, for it is then that serious and unforeseen upsets are most likely to occur. Among these are sudden death due to ventricular fibrillation or to abrupt cardiac standstill; rupture of the heart wall; various arrhythmias, particularly ventricular tachycardia and auriculoventricular heart block; and embolization to the lungs or to a peripheral artery, of which the source is a mural thrombus within one of the ventricular cavities. If the third week has been completed without mishap, the members of the patient's family may breathe more deeply and sleep more soundly, since they can be assured that the outlook for recovery is favorable. But the depth of the physician's sigh of relief, even at this time, is modified by his estimate of the severity of the damage to the heart. Familiarity with the amount of cardiac and coronary reserve which was present prior to the acute episode is of little help in making this estimate; clinical symptoms and signs, and the trend following the attack are the only dependable guides.

[•] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Clinic of the Presbyterian Hospital, New York. Lecture given as part of a Refresher Course in Cardiovascular Diseases, under the joint auspices of The New York Academy of Medicine and the New York Heart Association, November 25, 1942.

Shortly after occlusion has occurred it is impossible, even for the experienced observer, to make an accurate prognosis with respect to survival or the degree of subsequent functional recovery. As the days lengthen into weeks and the course can be charted, the details of the picture are gradually filled in. Usually, by the end of the second or third week, the case may be fitted into one of four main clinical categories; management of the stage of healing and the later period of convalescence will depend, in large measure, upon such classification. Viewed in this way the broad principles of treatment, rather than its minutiae, form the basis of procedure. The types of reaction are not sharply defined and some of their characteristics overlap; but they serve usefully in a practical sense and may be described briefly as follows:

Group 1. Critical, with shock. The outcome is always in doubt. Serious complications often occur. The heart is permanently crippled. Death, as a rule, is caused eventually by sequelae of the cardiac injury.

Group 2. Severe, with shock. The patient is gravely ill for several weeks. Convalescence is prolonged but there is partial, and often fairly good, functional recovery. It is unusual, however, for life to be prolonged for more than five years.

Group 3. Moderate, without shock. Although the attack may be stormy, the signs are favorable before the end of the second week. Functional recovery is good, sometimes complete, and there is frequently a long period of survival.

Group 4. Mild, often unrecognized. Some of these patients are ambulatory throughout. Discomfort at the time of the attack is not great or prolonged. Functional recovery is usually complete; but if the accident is ignored, life may terminate suddenly and unexpectedly before healing has taken place.

To formulate rules of action applicable to every contingency is manifestly impossible. Instead of attempting to present a formal catalogue of suggestions, it has seemed more profitable to cite the histories of cases illustrating each of the four categories and to discuss certain details of management relating to them.

THE CRITICAL TYPE, WITH SHOCK

Case 1. A trained nurse, aged forty-three years, claimed never to have known a sick day before the onset of the present illness. She had been a heavy smoker. While moving furniture in her apartment,

she felt a sudden, crushing, substernal pain, radiating down both arms, and this was followed by profuse perspiration. She vomited and thought she would die. A physician gave her large doses of morphine. Vomiting continued at intervals for thirty-six hours. An electrocardiogram was typical of early anterior infarction. She remained at home in bed during the next three weeks and while there, had repeated episodes of substernal pressure and shortness of breath. On the twentieth day, because there was no improvement, she was moved to the hospital.

On admission, she was still having pain and dyspnea, with a respiratory rate ranging from thirty to forty per minute. The rectal temperature was 102° F., the leukocytes were increased and the sedimentation rate was prolonged. There was slight cyanosis and numerous rales were heard at the bases of both lungs. The blood pressure was 130/90. Her condition was regarded as precarious and she was immediately placed in an oxygen tent.

During the following months there were repeated paroxysms of dyspnea and numerous hemoptyses, associated with pain in the chest. Dullness developed over both lower lobes and there were signs of congestive heart failure. The blood pressure fell to 106/52 and the venous pressure rose. Although there were fluctuations in the general condition, the trend was downward. The leukocyte count, which at the end of a month had returned to normal, again rose and remained in the neighborhood of 14,000, with 75 to 80 per cent polymorphonuclears. Fever continued, though it was not high. She was kept in the oxygen tent for three weeks. Digitalis was given in full doses and a daily maintenance ration was continued. Sedatives, in the form of bromide and luminal, were necessary during the daytime and were supplemented by hypodermic injections of morphine at night, and whenever discomfort became extreme. On several occasions, the increasing edema was lessened by intravenous injection of mercupurin, followed by theocalcin given by mouth, but improvement was only temporary. She became emaciated and weaker, and finally died of cardiac insufficiency eight months after the onset of illness.

The necropsy revealed adequate cause for the progressive failure. The heart weighed 430 grams. The anterior descending branch of the left coronary artery contained a large, yellow intimal plaque, which reduced its lumen by about one-half. The remainder of the



Fig. 1. Photograph of the heart of Case 1, showing the thinned, bulging wall of the left ventricle and the large intraventricular thrombus.

lumen was occupied by an organized thrombus. There was a large area of infarction involving the anterior part of the lateral wall of the left ventricle, as well as the interventricular septum. The infarct was healed but the wall of the left ventricle was thinned and bulging (Fig. 1). The other large branches of the coronary arteries showed advanced sclerosis, with numerous intimal plaques, some of which were calcified. The lumina were considerably reduced, but nowhere else was there complete obliteration.

Of striking interest was an enormous thrombotic mass occupying about half of the left ventricular cavity and situated in its anterolateral portion. It was firmly attached to the underlying endocardium. Almost half of the lower lobe of the right lung was solid, due to numerous infarcts, and there were scattered areas of infarction also in the lower lobe of the left lung. Arteriosclerotic scars were present in both kidneys.

Discussion. In this case, no therapy was effective. A large portion of the wall of the left ventricle was damaged and the function of the heart

was further impaired by the intraventricular clot. In addition to anoxemia caused by cardiac failure, there was deficient oxygenation of the blood as a result of extensive infarction of both lungs. The administration of oxygen in high concentration for several weeks,^{2,3} and attempts to combat congestive failure with the use of digitalis, mercupurin and theocalcin, failed to bring about lasting improvement, although life was prolonged for eight months. The chief aim of therapy was to maintain the patient in a state of relative comfort. The extent and nature of the pathological lesions determined the inevitably fatal outcome.

THE SEVERE TYPE, WITH SHOCK

Case 2. A business executive, aged sixty-one years, had been unusually active. For several months prior to the onset of the present illness, he had experienced moderate precordial pain on exertion, but kept at work. His attack of coronary occlusion was sudden and was followed by the classical symptoms of shock. He was placed immediately in an oxygen tent, where he remained for two weeks. The concentration was maintained between 50 and 60 per cent. There was a marked fall in blood pressure and the heart sounds were feeble. For a week there was doubt as to whether he would survive. Edema of the ankles and sacral region developed and he was, accordingly, given full doses of digitalis, namely one cat unit three times a day for one week. This was followed by disappearance of the edema, improvement in the character of the heart sounds and some elevation of blood pressure. He was kept flat on his back for four weeks and was then gradually permitted to sit up in bed for short periods, but did not get out of bed until the end of the eighth week. He developed severe pain in the right shoulder, which was partially relieved by the use of the infra-red lamp for twenty minutes twice a day, and by massage. He was first allowed to sit in a chair for fifteen minutes a day and then for gradually increasing periods. During the subsequent weeks, edema recurred and was treated successfully by digitalis and intravenous injections of mercupurin. A maintenance dose of digitalis was continued. At the end of four months, he went to Florida where he remained for twelve weeks. While in this warm climate, he walked for short distances and was permitted to take dips in a heated pool, never going above his depth. He was given light general massage three times a week. He was not permitted to begin work for six months after the onset of his illness.

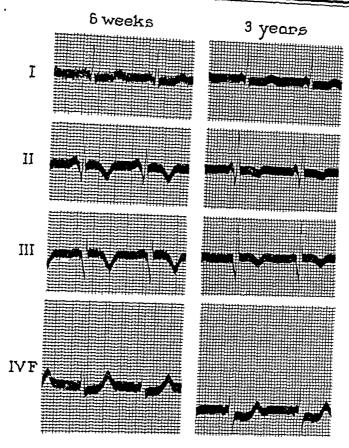


Fig. 2. Electrocardiagrams of Case 2 after the acute attack, taken at the intervals indicated. The second record was made two days before death.

There was no return of heart failure. The administration of digitalis was stopped. The blood pressure rose to normal levels. He became more active in business; when he was tired, premature beats of ventricular origin were noted. These were readily controlled by the use of quinidine sulphate, 3 grains taken three times a day after meals.

During the next three years, the patient took long winter and summer holidays. There was never any pain, although at times he was aware of a sense of pressure in the substernal region, both after effort and when he was under emotional stress.

Three years after his attack, while attending the wedding of a relative in another city, he partook freely of food and drink. That night he had an acute upset with digestive symptoms, and died suddenly a few hours later, undoubtedly as the result of another attack of coronary occlusion.

The electrocardiogram of this patient shows, in the first tracing

pictured, changes due to posterior infarction. The second record, taken three years later, shows these changes to be less in degree, but still present (Fig. 2). It was two days after this record was made that he died.

Discussion. The length of time that a patient should remain in bed after he has suffered an attack of cardiac infarction is variable. It is now the usual practice to make it six weeks; but this time may be and should be varied according to the circumstances in each case. What are some of the guides which help in reaching a decision? When there have been symptoms of shock at the onset, this period should not be shortened. When there have been signs of congestive failure it should be prolonged to a point at which all such signs have disappeared. There is pathological evidence that small infarcts heal almost completely in a month; larger infarcts require up to two months and there are instances in which areas of necrotic muscle may remain longer as foreign bodies in the midst of myocardial scars.4 The leukocyte count rises promptly following occlusion and is increased as the area of necrosis grows larger. On the average, and in the absence of complications, leukocytosis disappears in the course of five days. One of the best guides to the rate of healing of an infarct is the sedimentation rate of the erythrocytes.5 This usually does not rise significantly until the third or fourth day, reaching its peak between the fourth and eighth days. It reflects delicately both healing and any extension of the process. In the average case, it does not return to normal for about a month. When it remains elevated longer than this, it is well to suspect either incomplete healing, the presence of an intracardiac thrombus (as was described in Case 1), or the occurrence of some complication, such as pulmonary infarction. As a general rule, it is wise to keep the patient in bed until the sedimentation rate has reached a normal level. The effect of a known factor which might modify the reading, as for example, cystitis, must be discounted.

The rate of the heart is another useful guide. Usually this returns to normal in the course of ten days. Persistent tachycardia, particularly if associated with a diastolic gallop rhythm, is an index of severe cardiac damage and calls for more than the usual period of bed rest.

When the patient first gets out of bed, it is helpful, in order to prevent the collection of blood in extremities grown flabby from disuse, to apply Ace bandages to the feet and legs. These may be put on

before the patient leaves his bed and removed after he has returned to it; continue bandages during the first week that the patient is up.

A painful shoulder following coronary occlusion is not uncommon.⁶ It is not due to a local lesion, but is probably dependent upon afferent impulses from the heart which stimulate neurones whose fibers form part of the brachial plexus. There is tenderness and limitation of motion, but usually there are no changes in the x-ray picture, either in the joint or in the supraspinatus tendon. The pain may persist for weeks and sometimes for months. It sometimes causes discomfort at night, when the patient is awakened by rolling over on the tender area. The left shoulder is more commonly affected than the right, but the right is not immune. Heat, in the form of diathermy or the infra-red lamp, massage and passive movement afford some relief. There is a tendency for discomfort gradually to abate.

Guidance during late convalescence and during the years that follow requires understanding and patience on the part of the physician. Activities must be curtailed and a regimen outlined because a permanent injury has been done to the heart. Of greater importance is the fact that, in most instances, the coronary arteries outside the area of the healed infarct are sclerotic in varying degrees. On the other hand, many of these persons are active men, engaged in carrying on important affairs, who are eager to return to work. To do justice to both the individual and his disability furnishes a problem worthy of serious and careful consideration. Each case must be decided according to its own peculiar circumstances, which include personal characteristics, occupation, economic status and the condition of the heart. The presence of significant hypertension calls for greater conservatism than when the pressure is normal. The guiding principle should be to allow as much freedom of activity as is consistent with safety and good judgment. This, to be sure, is an indefinite suggestion; but specific advice rests upon so many varying factors that generalizations are neither feasible nor wise. Happily, in many instances, patients are able to do more, without discomfort or apparent harm, than at first appears possible.

THE MODERATE TYPE, WITHOUT SHOCK

Case 3. A male executive, aged forty-seven years, had had twinges of substernal pain for many years, but more marked for the few weeks preceding the onset of the present illness. He was a heavy cigarette

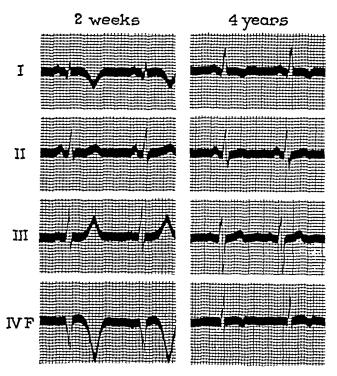


Fig. 3. Electrocardiograms of Case 3 after the acute attack, taken at the intervals indicated.

smoker. An electrocardiogram taken six months before the acute upset was normal, and he had been told that his discomfort was due to tobacco poisoning. The onset was acute, in the early morning. The pain was only of moderate severity and was not followed by shock. The electrocardiogram was typical of anterior infarction (Fig. 3). The leukocyte count was 20,000 with 88 per cent polymorphonuclears. The sedimentation rate, which reached a peak of 80 mm. in one hour on the seventh day, returned to normal at the end of the sixth week. He was kept in bed for seven weeks. There was no further discomfort in the chest after the initial pain had been controlled by morphine, and convalescence was uneventful. He was allowed to take a few steps on the fourth day out of bed. He did not attempt any work for four months and began by short sessions at his desk, at home. During the second summer, eighteen months after the attack, he was permitted to play golf on a level course, and did so without apparent injury to the heart. He started with a few holes and gradually worked up to eighteen. He has taken two drinks of alcohol daily.

It is now four years since the attack and he is working actively. He still rests for an hour after luncheon. After having gotten on without cigarettes for six months, the craving became too strong and he resumed his old habit at the rate of twenty or more each day.

The question of smoking almost invariably comes up for discussion. If the patient can give up tobacco entirely without hardship, it seems probable, though it is only fair to add, unproved, that he will fare better. On the other hand, many of these individuals derive a good deal of pleasure and emotional stability from smoking in moderation. By moderation, is meant from six to ten cigarettes a day. Two or three thin, mild cigars or three or four pipefuls of tobacco may be considered the equivalent of the given quota of cigarettes. The action of tobacco on the circulation appears to be a highly individualized matter. Some persons are susceptible to its effects, whereas others smoke freely without demonstrable harm. If a patient notices cardiac pain, palpitation or extrasystoles after smoking, it is well for him to stop entirely or cut down materially. Occasionally the "denicotined" brands appear to be tolerated better; but it is doubtful whether such slight differences in nicotine content are important.

Coffee, except in sensitive subjects, does no harm. Sometimes it causes premature beats, tachycardia or even cardiac pain, and should then be discontinued. It may be replaced by Sanka. It is well to remember that a cup of strong tea contains about as much caffeine as the average cup of coffee.

No matter how complete the degree of recovery, it is unwise to permit indulgence in violent sports, such as squash, tennis, vigorous gymnastic exercises or swimming for long distances. Ideal forms of recreational activity are walking, golfing on a level course or horseback riding. Swimming slowly and not too far is likewise permitted; but to fight breakers in a heavy surf is inadvisable. When exercise is limited because of occupation or other circumstances, light, general massage two or three times a week serves to maintain tone in the muscles and peripheral circulation.

If attacks of anginal pain appear with the resumption of activity, nitroglycerine should be taken freely, not only for relief but to prevent discomfort when some necessary activity or stress is anticipated. To prevent nocturnal attacks, erythroltetranitrate or mannitol hexanitrate, prevent nocturnal attacks, erythroltetranitrate or mannitol hexanitrate, grain tablet taken just before retiring, will often aid in securing un-

disturbed sleep. The prolonged vasodilator action of these drugs is especially helpful in the presence of hypertension. The value of the xanthine derivatives as coronary dilators, when given by mouth, is still disputed. Observations made in our laboratory on patients indicate that administration of one of these drugs is clearly helpful in certain cases.^{5,0} Our studies have been made chiefly with aminophyllin, given in a dose of 3 grains, three or four times daily. Sometimes smaller amounts are effectual. Administration should be continued over a period of months if painful seizures become fewer and less severe. It is difficult to select favorable subjects in advance and clinical trial is usually required. It seems likely that the drug acts largely by preventing or relieving coronary spasm; hence it is in the cases with less advanced lesions that the best results may be expected. The combination with aminophyllin of phenobarbital and a member of the atropine series, sometimes serves more effectively than any one of these alone.

In my hands, papaverine, given by mouth, even in large doses, has been worthless. The same may be said of the various organ and tissue extracts, whether given orally or by injection.

There is a small group of patients who suffer so intensely from anginal pain that some form of surgical therapy is justified. This is not the place for a consideration of the various procedures which have been employed. Accumulated experience warrants the conclusion that paravertebral sympathetic block with alcohol is the safest of these measures; when done by a skilled operator, it is effective in about 75 per cent of cases.¹⁰

Should it become necessary to perform a major surgical operation, such as cholecystectomy, the patient who has recovered from cardiac infarction stands it surprisingly well. If he is subject to congestive failure, the risk is clearly increased. After a preliminary dose of avertin, inhalation anesthesia may be begun with gas and oxygen, with emphasis to the anesthetist on plenty of oxygen. The operation is then continued under the influence of ether. When the margin of cardiac or coronary reserve is small, the postoperative use of an oxygen tent is helpful.

May the patient with a healed cardiac infarct fly or take up his residence at a high altitude? Provided there have been no symptoms or signs of congestive failure and there are no attacks of anginal pain or these are induced only after severe exertion, the answer is in the affirmative. During the ordinary aeroplane flight a height of 12,000 or

13,000 feet is rarely exceeded and the degree of anoxia produced at this altitude appears to be well borne. For example, a man of forty-six, who had his attack of coronary occlusion eight months ago, recently flew to Mexico City, remained there at an altitude of 7800 feet for two weeks and flew back to New York. During the flight the maximal altitude attained was 13,000 feet. He was cautioned against strenuous exertion while in Mexico. The transaction of business there tired him more readily than usual but he experienced no pain or dyspnea and there were no later ill effects.

Another patient, at the age of seventy-one, had a mild attack due to occlusion of an anterior branch, and made a splendid recovery. Three years later, long after the form of the electrocardiogram had returned to normal, he still noted a feeling of tightness in his chest on walking rapidly, but discomfort was not of sufficient severity to require the use of nitroglycerine. He was eager to spend the summer on his Western ranch at an altitude of 9200 feet and, with some trepidation on my part, permission to do so was given. While there, he walked and rode horseback without any unpleasant sensation in his chest. For the past four summers this experience has been repeated. Now, at the age of seventy-seven, he is convinced that he feels better in the mountains of Colorado than on the streets of New York.

Case 4. This case is included in order to indicate how failure to enforce adequate rest during the early stages may be followed by disastrous consequences. A forty-four year old liquor salesman for some years had noticed dyspnea on running up a flight of stairs. There had been no cardiac pain. Four weeks before his admission to the hospital, he developed a heavy feeling in his chest and a few hours later, during the night, experienced a severe pain beneath the sternum, radiating down the left arm. His physician gave him a sedative by hypodermic injection. Four days later he had a second, similar attack. He was kept in bed for ten days and then was allowed to get up and go about. During the next fortnight he became short of breath and had anginal pain radiating to the left arm.

He was admitted to the hospital exactly four weeks after his initial attack. The electrocardiogram was characteristic of an anterolateral infarct. There were signs also of a small pulmonary infarct in the left lower lobe. The sedimentation rate was elevated, but the leukocyte count was normal. There was slight fever for the first week, up to

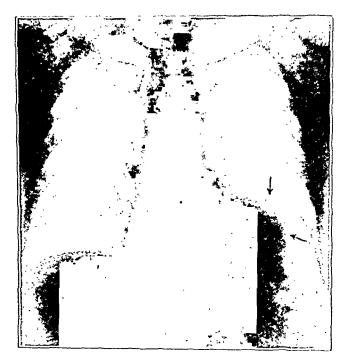


Fig. 4. Teleroentgenogram of Case 4. The arrows point to the cardiac ancurysm, which was first photographed four weeks after the occurrence of acute coronary occlusion.

100.4° F. The blood pressure was 100/70. It fell gradually to 80/50. He experienced a good deal of pain in the left shoulder. An x-ray film of the heart showed a large bulge in the border of the left ventricle, which subsequent roentgenological examinations, both fluoroscopic and kymographic, proved to be a cardiac aneurysm (Fig. 4).

This patient has been followed in the clinic for eight years. He has never been able to resume work. He has suffered from severe anginal pain and, at times, from bouts of congestive failure. There have been two subsequent attacks of coronary occlusion with signs of cardiac infarction, both mild, but requiring care in the hospital. The appearance of the aneurysm has remained essentially unchanged.

Discussion. A cardiac aneurysm may develop even when the initial rest period has been carefully supervised. But any added effort made while the infarct is soft will tend to aggravate such a tendency. There is experimental evidence to support this statement.¹¹ In normal dogs, cardiac infarction was produced by ligation of a coronary artery. In those animals allowed to rest for six days before being exercised on a

motor-driven treadmill, a small, firm scar was produced. In others, made to run sooner, a thin, bulging area was observed in the affected portion of the ventricle. The rate of healing in the myocardium of the healthy dog is clearly faster than in the diseased human heart.

It is logical to enforce complete inactivity long enough to let edema about the lesion subside, to permit absorption of the necrotic muscle and its replacement by scar tissue, and to encourage the development of a collateral circulation. The crucial period is during the early weeks and no amount of curtailment of activity later can compensate for rest which is lost at a time when it counts most. The patient who is comfortable at the end of a week or two often finds it difficult to understand why he is urged to lie so quietly and is still fed by the nurse. Attention should be focussed on his future welfare and he must be induced to sacrifice present desires for a chance to recover as completely as possible. There can be no compromise; for in restraint during this early period lies the core of successful management.

In the case described the duration of rest was only two weeks and the aneurysm of the ventricle was seen in the x-ray film four weeks after the acute occlusion. Although kept in bed for four weeks after admission to the hospital, the subsequent course made it clear that the damage already done was irreparable. Some patients with a thin and bulging ventricular wall are surprisingly well and active, considering the nature of their disease. Others, like this man, are incapacitated and uncomfortable, although they survive for a number of years.¹²

THE MILD TYPE

Case 5. A retired lawyer, seventy years of age, for two years had experienced shortness of breath on effort. One evening he began to retch and vomit, and felt a sense of constriction in the lower part of the chest. This sensation lasted three or four hours and was accompanied by profuse sweating. The next day he felt weak, but comfortable. Three days later, he went to another city to consult a gastroenterologist, who had been treating him for a number of years for digestive disturbances. He was given a mixture of antacids and sent home. On climbing the stairs at the Pennsylvania Station at the termination of his return trip, he was short of breath and had pain in his chest. He remained at home for a few days and then attended to his affairs downtown. He was seen three weeks after the onset, because he wanted a check-up before going to the country for the summer.

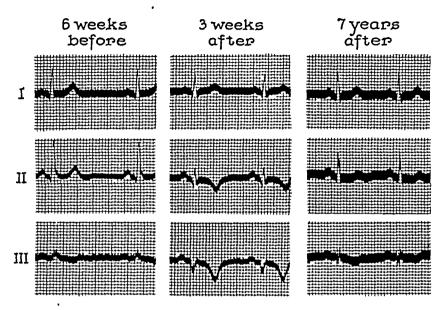


Fig. 5. Electrocardiograms of Case 5 before the acute attack and after its occurrence, taken at the intervals indicated.

The heart was not enlarged. The first sound at the apex was very weak. The blood pressure was 114/62. The electrocardiogram was typical of posterior infarction (Fig. 5). It would have been difficult at this point to persuade the patient to go to bed for he was perfectly comfortable and could hardly believe that his heart was affected. He was permitted to go to the country by motor on the following day, accompanied by a nurse. He was carried to his room on the second floor and remained on that floor for four weeks. He arose late in the morning and rested for two hours each afternoon. The prescribed month of rest was taken with equanimity. Resumption of a more active life was very gradual. No cardiac medication was prescribed.

These events took place more than seven years ago and the patient is now seventy-seven years of age. He still takes part in various civic and philanthropic affairs. There is no cardiac discomfort. The electrocardiogram shows minor residual changes.

Discussion. In this instance, coronary occlusion occurred in an elderly man without hypertension and with a heart of normal size, who for two years had had symptoms due to coronary insufficiency. In all probability, an adequate collateral circulation had developed so that infarction was followed by minimal symptoms and only slight functional derangement of the heart. For three weeks the nature of the illness

was unrecognized and he might well have recovered completely with-

out ever knowing that the upset was cardiac and not digestive in origin.

If such a case is seen immediately after the onset, a period of rest in bed for three or four weeks usually suffices. Fever lasts only a few days and is not high. The leukocyte count may be only nine or ten thousand; and the sedimentation rate returns to normal within two or three weeks. In contrast to these slight disturbances, the changes in the form of the electrocardiogram are relatively of greater magnitude. The degree of distortion of the complexes is not a guide as to the severity of the lesion or the prognosis. Minimal alterations may be observed shortly before sudden death; bizarre and greatly distorted sequences occur in the presence of a benign clinical picture. The electrocardiogram may be expected to show change in serial records, often in the direction of normal. But such change is not to be used as an important aid in management, for it may continue for weeks or months, and even for years. A sudden shift in form suggesting an advancing lesion, even in the absence of symptoms, is a signal for caution and watchfulness.

The course of action will depend upon the appearance of other signs.

Case 6. Not all of the mild cases are as fortunate as the one whose history has just been given. A stock broker, aged fifty-eight, had been a remarkably healthy man. His father and one brother died of heart disease. While in the south playing golf, he experienced substernal oppression and indigestion. He continued to play and had four seizures on the course. He was finally taken home in an ambulance. The pain was not severe, but he felt limp. He remained in bed for five days and then was taken to a hospital, where an electrocardiogram was made which, according to the report, showed inversion of T1 and T2 and was interpreted as indicating coronary occlusion. He remained in bed for a week and then came home to New York, by train. Because he felt perfectly well he went to his office. Nocturnal oppression and indigestion recurred. Three weeks after the onset he had a sense of pressure which lasted all day; and it was four days later that I saw him.

On examination, the heart was not enlarged. The sounds had a thin, sharp quality. The blood pressure was 124/82. The electrocardiogram showed the T waves in Leads I and II to be of low amplitude and diphasic. Although it was almost four weeks after his initial symptoms, he was having attacks of prolonged substernal oppression, indicating that the pathological process in the heart was still active. He was advised to go home to bed under the care of nurses and this recommendation was made in a letter to his physician. The patient refused and continued to attend to his business downtown. At the end of two weeks, he called on the telephone to poke fun at the diagnosis and laugh at the advice which had been given. Ten days later, and seven weeks after the first appearance of discomfort, his obituary appeared in the morning paper under the headline, "Retired Broker Dies Unexpectedly at His Summer Home. Heart Disease Is Fatal."

Discussion. When the diagnosis of cardiac infarction has been made on adequate evidence and symptoms persist in the form of frequently recurring pain or paroxysmal dyspnea, the patient should be put to bed. A major occlusion cannot always be prevented, for even at rest, the occlusive process may extend. But under stress, involvement of only a small branch can cause acute coronary insufficiency and initiate ventricular fibrillation; it is probable that such a mechanism was responsible for sudden death in this instance.

COMMENT

In the title of this paper it has been stated, with intent, that consideration would be given to the management of the patient; no mention was made of the treatment of his disease. Impairment or stoppage of the flow of blood through a coronary artery causes injury to that portion of the myocardium which receives its nutrition from the affected vessel. The processes of repair which follow are the reactions of the tissues to that injury. They are adaptive reactions designed to promote healing of the lesion and provide new channels of circulation in its vicinity. Unfortunately, they do not always accomplish this end. There is no form of medicinal therapy which directly modifies the structural changes which take place. Surgical procedures designed to form a new blood supply to the heart, such as the transplantation of a pectoral muscle or the injection of foreign substances into the pericardial sac, have not yet proved either their safety or effectiveness. The chief aims of the physician, therefore, are to safeguard the heart during its convalescence by lessening its work and to aid in maintaining its adequate functional performance with drugs, when this may be necessary. After recovery from the acute upset the cardiovascular system must be protected, insofar as possible, from further injury and strain. Often, much that is helpful can thus be accomplished; but because the basic influences which modify the biology of atherosclerosis are at present beyond control, the disease progresses at its own rate and in its own way.

In his presidential address before the Congress of American Physicians and Surgeons in 1897, Dr. William H. Welch discussed "Adaptation in Pathological Processes." Both in content and form the paper is a classic, and forty years later was reprinted as a booklet by the Institute of the History of Medicine of the Johns Hopkins University. It is with quotation of the final paragraph that I shall conclude.

"The healing power of nature is, under the circumstances present in disease, frequently incomplete and imperfect, and systems of treatment based exclusively upon the idea that nature is doing the best thing possible to bring about recovery or some suitable adjustment, and should not be interfered with, rest often upon an insecure foundation. The agencies employed by nature may be all that can be desired; they may, however, be inadequate, even helpless, and their operation may add to existing disorder. There is ample scope for the beneficent work of the physician and surgeon."

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

October 1—The New York Academy of Medicine. ¶ Executive session. Reading of the Minutes. ¶ Papers of the evening—Scientific program under the joint sponsorship of The New York Academy of Medicine and its Section of Surgery and Section of Ophthalmology. ¶ Chemical Warfare as Affecting Civilian Population—a] Pulmonary irritants, Robert A. Kehoe, Research Professor of Physiology, College of Medicine, University of Cincinnati; b] Vesicants, Leon Goldman, Assistant Professor of Dermatology, College of Medicines, College of Medi

cine, University of Cincinnati; c] The effect of irritating and destructive gases and chemicals on the eye, Conrad Berens, Professor of Ophthalmology, New York University College of Medicine; Edward Hartmann, Formerly Chief of the Ophthalmologic Service, American Hospital of Paris, France. ¶ Report on Election of Fellows and Corresponding Fellows.

OOTOBER 29—The Harvey Society in affiliation with The New York Academy of Medicine. ¶The First Harvey Lecture —"The Significance of Labile Methyl Groups in the Diet and Their Relation to Transmethylation." Vincent Du Vignaud, Professor of Biochemistry, Cornell University Medical College.

NOVEMBER 5-The New York Academy of Medicine. ¶ Executive session: o'clock. a] Reading of the minutes; b] Report of Nominating Committee. ¶ Papers of the evening: Scientific program under the joint sponsorship of The New York Academy of Medicine and its Section of Medicine. Special Therapeutic Agents in Infections. al Gramicidin, René J. Dubos, George Fabyan Professor of Comparative Pathology and Tropical Medicine, Harvard University; b] Clinical application of gramicidin and penicillin, Chester S. Keefer, Wade Professor of Medicine, Boston University School of Medicine; cl Sulfonamide therapy in diseases of the intestinal tract, Warfield M. Firor, Visiting Surgeon, Johns Hopkins Hospital. Report on Election of Fellows.

November 19—The Harvey Society in affiliation with The New York Academy of Medicine. ¶ The Second Harvey Lecture, "Total Homeostasis," Curt P. Richter, Associate Professor of Psycho-Biology, Johns Hopkins University.

SECTION MEETINGS

October 6—Dermatology and Syphilology.

¶ Presentation of cases. ¶ Discussion.

¶ Executive session: Nomination and election of secretary.

Surgery—This Section held no meeting on its regular date as it combined with

the State Meeting of October 1.

October 6—Combined Meeting Neurology and Psychiatry and the New York Neurological Society. ¶ Presidential address, Neuropsychiatry in War Time, G. A. Blakeslee. ¶ Papers of the evening—a] Early laminectomy in spinal cord injuries, F. Kennedy, P. G. Denker, R. L. Osborne; discussion by E. J. King, Byron Stookey; b] Effect of Vitamin E therapy on the central nervous system in amyotrophic lateral sclerosis, Charles Davison; discussion by Tracy J. Putnam, I. S. Wechsler.

OCTOBER 8-Pediatrics. Reading of the minutes. ¶ Presentation of cases: Program arranged by Pediatric Service of Mt. Sinai Hospital-al An acute febrile illness with rash and leukopenia due to H. para-influenza, Alfred R. Florman (by invitation); discussion by Hattie Alexander (by invitation); bl A comparison between protamin and regular insulin in the young diabetic, Alfred E. Fischer, discussion by Frederick W. Williams; c] Idiosyncrasy to mercury in childhood, Murray H. Bass; d] The pathological kidney findings as compared with the clinical course of lipoid nephrosis in childhood, Jerome Kohn; discussion by Herman Schwarz, John D. Lyttle; el Management of pulmonary abscess in childhood, George Ginandes (by invitation); discussion by Harold Neuhof. & General discussion. Executive session.

Ophthalmology—This Section held no meeting on its regular date but combined with the Stated Meeting of October 1.

OCTOBER 27-Obstetrics and Gynecology. [Executive session-a] Reading of the minutes; b) Nomination and election of secretary. Papers of the evening-al Syphilis in pregnancy-End-results in treatment, Mortimer Dudley Speiser; b] Highlights in the diagnosis and treatment of gonorrhea in women (Public Health viewpoint), Adolph Jacoby; cl Gonorrhea-diagnosis and treatment, R. Gordon Douglas (by invitation). & General discussion-Opened by David Nye Barrows and Louis Chargin-The Section regrets the resignation of Locke L. Mackenzie as Secretary due to his entering the navv.

Genito-Urinary Surgery—Medicine—Orthopedic Surgery—Otolaryngology—These Sections held no meeting in October because of conflict with meeting dates of the Graduate Fortnight.

November 4—Dermatology and Syphilology.

¶ Presentation of cases—a] From the
Skin and Cancer Unit of the Post-Graduate Medical School; b] Miscellaneous
cases. ¶ Discussion. ¶ Executive session.

November 4—Historical and Cultural Medicine. Reading of the minutes. ¶ Papers of the evening—Public Health in the City of New York—a] Introduction, by James Alexander Miller; b] Retrospect, by E. H. L. Corwin and Charles Bolduan; c] Glimpses of the future, by Ernest L. Stebbins (by invitation). ¶ General discussion.

Novemer 6—Surgery. Reading of the minutes. ¶ Case presentation — Unusually large adenoma of the adrenal gland, Francis X. Timoney. ¶ Case report—Congenital absence of common bile duct, Stanley J. Brady (by invitation). ¶ Papers of the evening—a] An eight-year review of ruptured peptic ulcers at St. Vincents' Hospital, with special reference to the local use of sulfonamides, Francis X. Timoney; discussion by Constantine MacGuire; b] Reconstruction of the common bile duct, Raymond P. Sullivan. ¶General discussion. ¶ Executive session.

November 10—Combined meeting Neurology and Psychiatry and the New York Neurological Society. Papers of the evening—a] The selective use of electro-shock therapy as an adjuvant to psychotherapy, Herman Selinski; discussion by Bernard B. Glueck and R. B. McGraw; b] Primary diffuse sarcomatosis of meninges, M. P. Rosenblum (by invitation), and Lewis D. Stevenson; discussion by Joseph H. Globus; c] Limitations of psychoanalytic therapy, Herman Nunberg; discussion by A. A. Brill and Bertram D. Lewin.

November 12—Pediatrics. Reading of the minutes. ¶ Round Table Discussion—

Eczema in infants and children, Robert A. Cooke, Marion B. Sulzberger, Anthony C. Cipollaro and Howard H. Mason. ¶ General discussion.

NOVEMBER 16—Ophthalmology. ¶ Instruction Hour: 7.00 to 8.00 o'clock-War injuries of the eye, Edward Hartman (by invitation). ¶Executive session—Reading of the minutes. | Presentation of cases-al Bilateral metastatic carcinoma of the choroid, Arthur J. Bedell; discussion by Arnold H. Knapp; b] Neurodermatitis with cataract, Clyde McDannald; discussion by Truman L. Boyes. Papers of the evening-a] Immediate and late reoperation for glaucoma, Willis S. Knighton; b] Histologic causes for failures in glaucoma operations, . Brittain F. Payne; discussion by A. B. Reese.

Section of Medicine—The Section of Medicine did not hold its regular meeting on November 17, as it combined its scientific program with that of the Stated Meeting on November 5.

NOVEMBER 18 — Genito-Urinary Surgery. Reading of the minutes. ¶ Case reports -a] Enormous prostatic diverticulum, E. King Morgan; b] Diverticulum of posterior urethra with stones, O. P. Schoenemann; c] Reflex renal shutdown after prostatic resection, T. A. Morrissey (by invitation). Papers of the evening-a] Prevention of renal obstruction on massive sulfadiazine therapy, Ole Jensen (by invitation); b] Further experiences with vitallium tubes in the urinary tract of the dog, Jere Lord (by invitation); c] Hyperplastic change at the vesical neck in the female, Joseph A. Hyams and Sidney Weinberg (by invitation). ¶ General discussion. ¶ Executive session.

November 18—Otolaryngology. Reading of the minutes. ¶ Papers of the evening—a] Granular cell myoblastomas of the external auditory meatus, Franz Altmann (by invitation); b] Principles of

diagnosis and treatment of allergy as related to otolaryngology, French K. Hansel, St. Louis, Mo. (by invitation); discussion by Marvin Jones and R. C. Grove. ¶ General discussion. ¶ Executive session.

November 20-Orthopedic Surgery. Reading of the minutes. | Presentation of cases-a] A case of disability of the knee joint, Alvin Hulnick (by invitation). ¶ Papers of the evening—a] Recurrent dislocation of the patella, Walter Thompson (by invitation); discussion by Lewis Clark Wagner; b] The repair of the ruptured crucial ligaments of the knee, Fred H. Albee; c] "Hey-Groves' Operation for Repair of Crucial Ligaments"-Motion picture and discussion of the subject, Arthur Krida. ¶ General discussion. ¶Executive session.

NOVEMBER 24—Obstetrics and Gynecology.

¶ Executive session — Reading of the minutes. ¶ Case report — Pregnancy complicated by a large myoma, Arthur F. Wright (by invitation). ¶ Round table discussion—The menopause and its problems, Frederick C. Holden, Chairman, Harvey B. Matthews, Samuel H. Geist, and Ralph L. Barrett. ¶ General discussion.

AFFILIATED SOCIETIES

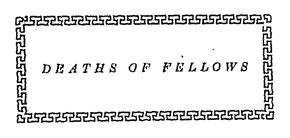
October 29—New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Papers of the

evening—Medically unimportant autopsy findings which are likely to be of paramount interest from a medico-legal standpoint, Alan R. Moritz (by invitation). ¶Executive session—A vote was taken on the proposed revision of the Constitution.

New York Roentgen Society in affiliation with The New York Academy of Medicine. Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October.

November 12—New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Presentation of cases—a] Meningioma with invasion of the pituitary gland, John J. Larkin (by invitation); b] Agenesis of lung—Report of case, Charles T. Olcott; c] Acute febrile anemia in thrombocytopenia with generalized platelet thrombi, Paul Klemperer. ¶ Paper of the evening—The mechanism of jaundice in carcinoma of the pancreas, Naomi Kaplan (by invitation) and Alfred Angrist. ¶ Executive session.

NOVEMBER 16—New York Roentgen Society in affiliation with The New York Academy of Medicine. ¶ Papers of the evening—a] Non-luetic aortic aneurysms, M. F. Steinberg; b] Atypical coarctation of the aorta, A. Grishman; c] Roentgen appearance of right heart enlargement, M. L. Sussman; discussion by A. H. Blakemore (by invitation) and Ernst Boas (by invitation). ¶ Executive session.



ALLEN, THEOPHILUS POWELL: 16 East 90 Street, New York City; born in Milledgeville, Georgia, July 24, 1896; died in New York City, January 27, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1923; elected a Fellow of the Academy November 6, 1930.

Dr. Allen was associate attending physician to St. Luke's Hospital; assistant attending physician to the Neurological and Presbyterian Hospitals; a Fellow of the American Medical Association, and a member of the National Gastroenterological Association, and the State and County Medical Societies.

Bolor, Hermann Johannes: White Plains, New York; born in Neuentempel, near Berlin, Germany, June 24, 1856; died in St. Petersburg, Florida, January 12, 1943; graduated in medicine from New York University of the City of New York Medical Department in 1879; elected a Fellow of the Academy June 5, 1884.

Dr. Boldt was emeritus professor of gynecology at the New York Post-Graduate Medical School, where he had been professor of gypecology from 1891 to 1917; consulting gynecologist to the New York Post-Graduate Medical School and Hospital, Stuyvesant, Polyclinic, St. Vincent's, Beth Israel and Union Hospitals. He was one of the founders, formerly a member of the Board of Governors, and Fellow of the American College of Surgeons, a member of the Southern Surgical Society, an honorary member of the American Gynecological Society, and Gynecological Society of Great Britain, a member of the National Society of Sciences, the New York Academy of Sciences, the Association of Military Surgeons,

and the Royal Society of Medicine, London.

Dr. Boldt was the inventor of an operating table for abdominal surgery which won a medal at the Paris exposition in 1900, and was known as an extensive investigator on the physiologic action of cocaine and gynecologic pathology.

Morris, John Harold: 535 Park Avenue, New York City; born in Cortland, New York, July 29, 1889; died in New York City, November 30, 1942; graduated in medicine from Cornell University Medical College in 1914; elected a Fellow of the Academy January 3, 1924.

Dr. Morris was associate clinical professor of surgery at New York University College of Medicine and visiting surgeon to the Bellevue Hospital, St. Vincent's Hospital and the Goldwater Memorial Hospital at Welfare Island, formerly the Hospital for Chronic Diseases. He was a diplomate of the American Board of Surgery, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the New York Surgical Society, and a member of the State and County Medical Societies.

Schiller, Abraham Noah; 27 West 72 Street, New York City; born in New York City, April 15, 1884; died in New York City, December 17, 1942; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1907; elected a Fellow of the Academy May 3, 1923.

Dr. Schiller, one of the founders of the Jewish Memorial Hospital, was honorary chairman and chairman of the medical board, consulting otolaryngologist and for many years chief of the department of otolaryngology at that institution; consulting otolaryngologist and attending physician in the ear, nose and throat division of the New York City Hospital, Welfare Island; a member of the American Academy of Ophthalmology and Otolaryngology, the American Medical Association and the State and County Medical Societies.

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF THE NEW YORK ACADEMY

OF MEDICINE



MAY, 1943

MULTIPLE SCLEROSIS AND, "ENCEPHALOMYELITIS"

TRACY J. PUTNAM

Professor of Neurology and Neurosurgery College of Physicians and Surgeons, Columbia University

HISTORICAL

HISTORICAL

Professor of Pathology at the University of London, published an installment of his handsome atlas of pathology² containing a picture and installment of his handsome atlas of pathology² containing a picture and installment of his handsome atlas of pathology² containing a picture and installment of his handsome atlas of pathology³ containing a picture and installment of his handsome atlas of pathology³ containing a picture and installment of his handsome atlas of pathology³ containing a picture and installment of his handsome atlas of pathology at the University of London, pathology at the University were spotted with greyish areas of atrophy of irregular shape, and in the lumbar region was an area of softening. No history was available.

Within a year or two, the great French pathologist, Cruveilhier, described three similar specimens in his own atlas of pathology,3 also coming out in installments. His description was far more complete than Carswell's and in addition, he was able to supply two typical case histories.

During the following twenty years, there were sporadic anatomical and clinical studies of the various types of degeneration of the spinal

From the Department of Neurology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York City. Read October 20, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine,

cord. An example is a clearly written pathologic report by a young Philadelphian, Dr. S. Weir Mitchell. But little progress was made toward a practical working knowledge of this peculiar disease, until the publication in 1868 of a clear, concise review of the literature and description of original cases by Jean Marie Charcot. He definitely fixed the name of the disease—"Sclérose en plaques disseminée"—and gave a succinct account of the pathologic changes, which is in certain ways better than the descriptions in some modern textbooks. He emphasized the haphazard distribution of the lesions, their sharp outlines, the breakdown of myelin sheaths, the preservation of a variable proportion of axis cylinders, the glial scar, and the thickening and obstruction of vessels.

His description of the clinical picture was clear, though oversimplified. It was based on the illness of a servant girl in his own household, who finally came to autopsy at the Salpêtrière. Her symptoms nystagmus, intention tremor and scanning speech—constitute the triad familiar to every medical student. In a later work (1879), Charcot⁵ went further, and called attention to the milder cases, which we now recognize as the commonest type.

Charcot's lectures on neurology became known all over the world, and doubtless as a result, a steadily increasing number of cases of multiple sclerosis began to be reported. In the last century, it was considered to be a rare disease, but modern statistics show it to be a common one, especially if we include its acute forms, usually known as encephalomyelitis, acute transverse myelitis and optic neuritis.

Prevalence of unultiple sclerosis and related disorders: Owing to variations in standards of diagnosis and in local prevalence, it is extremely difficult to estimate the incidence of multiple sclerosis. A survey in Switzerland showed 7 per 10,000 in certain localities. In recruits examined for the last war, the incidence was about 1 per 10,000 (including rejections and discharges). The last figures for selectees in the New York City area showed a rate of rejection of about 6 per 10,000 for multiple sclerosis, encephalitis and myelitis. These figures are probably all on the low side, for recent experience shows that the diagnosis is more often missed than erroneously made. With the use of modern refinements in diagnosis, multiple sclerosis and encephalitis need no longer be "wastebasket" categories. It is clear that in this locality at least, multiple sclerosis is by no means a rare disease.

There is a pronounced difference in the *local* incidence of multiple sclerosis. It is common in the Baltic countries, Scotland, the North Atlantic seaboard and the Great Lakes region. It is rare in the Mediterranean countries and our own South, and almost unknown in China, Turkey, India and Japan.

Scope of the category of demyelinating diseases: Multiple sclerosis as ordinarily defined, is characterized pathologically by the existence of glial scars scattered throughout the nervous system. There is now practically complete agreement among neuropathologists that the gliosis is secondary to tissue damage, and that each lesion goes through an acute stage (Marburg⁸). It is usually agreed that the acute lesions are marked by edema and local glial proliferation and perivascular infiltration.

Beyond this point, there are many differences of opinion, and here I can do no more than express my own. I believe, with Marburg,8 Ferraro,9 Juba10 and a few others, that the disorders characterized by scars interspersed with acute lesions are but the chronic relapsing form of the acute demyelinating diseases (Figures 1, 2). This group of diseases includes the type known as post-infectious and disseminated encephalomyelitis, Schilder's disease, diffuse sclerosis, neuromyelitis optica, acute transverse myelitis, and "idiopathic" optic and retrobulbar neuritis.11 The histopathology of these disorders is fundamentally uniform;9,10,11,12 the differences are in location and intensity of the lesions Naturally, an acute transverse lesion of the cord is more apt to be fatal than one in the optic nerve; naturally also, massive lesions of both hemispheres (Schilder's disease, diffuse sclerosis) is more devastating than small isolated plaques, but the type and varieties of tissue reaction are the same. The acute disorders comprise the great majority of the cases of "encephalitis" encountered in practice; the specific encephalitides, due to known infective viruses, present a wholly different aspect, pathologic and clinical, and are at present rare in this region.

Since there is no agreement whatever among neuropathologists as to the etiology of these disorders, I shall postpone consideration of it until after a sketch of their clinical manifestations, which should be taken into account in deciding among rival theories.

Predisposing factors—Infections: Taking the demyelinating diseases as a group, it is clear that a sudden or subacute onset is common and often apparently precipitated by exogenous factors. This is most clearly

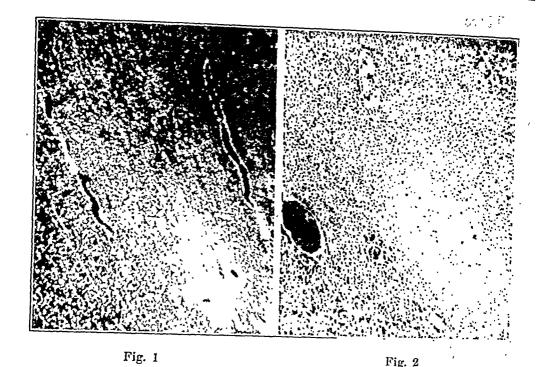


Fig. 1—Multiple sclerosis. A small, early lesion, consisting of loss of myelin, damage to axis cylinders, and glial proliferation. Note the tortuosity and engorgement of the veins draining the area. Mallory's connective tissue stain.

Fig. 2—Postvaccinal "encephalitis." Early demyelinating lesion. Note the similarities to Figure 1. The thrombosis of the neighboring vessels is obvious. Mallory's connective tissue stain.

seen in the post-infectious "encephalomyelitides." In the post-vaccinal form, the onset of the "encephalitis" coincides with the height of immunity in most cases; that is, it occurs on the 11th day in most cases. In post-measles "encephalitis," the onset of cerebral symptoms usually occurs in five days from the outbreak of the rash. While these two types of post-infectious "encephalitis" are the most widely recognized, they are not the most common. Actually, the banal infections of the respiratory tract—pneumonia, sinusitis, tonsillitis—are more often the apparent precipitating cause of optic neuritis, "encephalomyelitis," acute transverse myelitis, neuromyelitis optica, and multiple sclerosis, than are any of the specific infectious diseases. 14

Examples should be familiar to all practitioners. An instance is the following:

J. M., a previously healthy medical student, developed a paronychia of the middle finger of the left hand in 1927. Three days later, he came down with a quadriplegia and symptoms of bulbar disease, and had to be tube-fed. There was an increase of

cells in the spinal fluid. A diagnosis of "encephalitis" was made. After a convalescence of several months, he considered himself entirely well and returned to work. Following a period of fatigue, he developed a paronychia on the other hand, and had a recurrence of the same symptoms. He recovered from this also, but with a residual limp and hemiataxia. He graduated from medical school and went into practice. Every year or so, he has an attack of sinusitis, and his weakness and ataxia reappear. Each attack leaves him slightly worse, and sometimes adds a new symptom, but he is still able to practice.

Syphilis should probably be included among predisposing infections. The incidence of serologic evidences of syphilis is slightly higher among patients suffering from multiple sclerosis, than in the population at large.

Trauma: Acute traumatic "encephalomyelitis" is a recognized disease entity, but it is relatively rare. Adler¹⁴ found two cases, compared with thirty following infections. The influence of injury is apparent in many cases of multiple sclerosis, however. Some striking examples are the following:

The R. sisters were identical twins, aged 27, who earned their living by tapdancing at night clubs. Shortly after finishing an engagement, one of them slipped and fell, landing on her buttocks. She was certain that she felt perfectly steady and normal up to the time of the fall; but at once slie felt a weakness of the legs, and a numbness up to the nipples. She had to be helped home. A neurologist was called, and found bilaterally positive Babinski signs. From that on, she ran an intermittent downhill course, finally presenting an unmistakable picture of advanced multiple sclerosis. The other twin remains in good health.

A female schoolteacher of 28 was brushed by a passing automobile and thrown down, but was not unconscious. She was unable to rise, and had to be taken to the hospital. There she was found to have a mild paraplegia, intention tremor and nystagmus. She had been incapacitated for three months when last seen.

Pregnancy and Menstruation: A fatal "encephalomyelitis" is apparently rare in pregnancy, but few women who have had retrobulbar neuritis or other manifestations of multiple sclerosis can pass through pregnancy and the puerperium without danger of an exacerbation. Initiation or exacerbation of multiple sclerosis occurred in 60 per cent of Beck's female patients who had borne children, and this corresponds with my own experience. Similarly, menstruation has an adverse effect, particularly in the terminal stages of the disease.

Thus, one woman (in whom the diagnosis was confirmed at autopsy) began to have irregular periods toward the end of her course. Preceding each one she would have a two days' fever, and become completely paralyzed, often unconscious. Each of these events marked a step downward in the progress of her disease, which was practically stationary between them.

Toxic Substances: "Encephalomyelitis," "myelitis" and multiple sclerosis are not infrequently precipitated by the administration of sera, vaccines, and certain chemicals. In a case in my collection, an acute paraplegia followed the day after a vaccination against typhoid fever

and similar cases are reported in the literature.¹⁷ The incidence of "encephalomyelitis" during the Pasteur treatment against rabies is about .04 per cent (Wilson¹⁸). Tetanus antitoxin¹⁹ (and experimentally tetanus toxin²⁰) have also apparently been responsible for the onset of multiple sclerosis. I have seen two cases in which relapses followed immediately upon administration of histamine. Perhaps the case of "encephalitis" following a burn, reported by Globus and Bender²¹ belongs in this category also. In animals, coagulants produce a similar picture.²²

Of inorganic substances, the injection of sulfanilamide has been followed by a typical "encephalomyelitis." Carbon monoxide poisoning has precipitated a progressive multiple sclerosis. Experimentally, repeated administration of potassium cyanide rather regularly brings about the characteristic pathologic changes. Lead poisoning has been found in multiple sclerosis, and excessive amounts of arsenic in cases of "encephalomyelitis." Finally, the typical "hemorrhagic encephalitis" produced by arsphenamine, and some of the cases of carbon monoxide and nitrous oxide poisoning, closely resemble post-infectious "encephalomyelitis."

Other Factors: Over-exertion, chilling, fright and emotion are often mentioned as precipitating causes of multiple sclerosis, and von Hoess-lin²⁸ gives some rather low figures of incidence. In the category of emotion (rather than of trauma) might go the cases in which lumbar puncture or venipuncture have apparently brought on exacerbations of an established multiple sclerosis. This I have seen.

Brickner and Brill²⁰ have cited cases in which dietary indiscretions or the use of a greatly restricted diet have been followed by relapses. This I have not happened to observe. The possible influence of diet will be considered under etiology.

Manifestations: There is no single syndrome that can be considered typical of multiple sclerosis and the demyelinating diseases. A great variety of symptoms may occur: Weakness or numbness of one or more extremities, tremor, ataxia, nystagmus, speech disturbances, emotional lability, retrobulbar neuritis or papillitis, with central scotoma, diplopia, disturbances of bladder function and the "electric phenomenon" are frequently found in both the acute and the chronic stages of the disease. Less well recognized are various psychoses, convulsions, decrease in potency, papillitis, symptomatic paralysis agitans, trigeminal neuralgia, sciatica and other neuritic pains, headache, mustrigeminal neuralgia, sciatica and other neuritic pains and science neuritic pains and science neurit

cular atrophy,³⁴ oscillopsia,³⁵ drowsiness, difficulty in swallowing, hemianopia, and aphasia. An outstanding review of the manifestations of multiple sclerosis may be found in Marburg's monograph.³⁶

In the acute, fulminating cases of "encephalomyelitis," fever, headache, convulsions, coma, stiffness of the neck, hemiplegia, oculomotor palsies, and acute optic neuritis are common (Adler³⁷).

The course of symptoms is often characteristic. They sometimes come on within a few minutes, or overnight. A patient may watch a scotoma develop, or be thrown down by a hemiplegia. Often, the onset is subacute, gradually increasing over days, sometimes with fever and leukocytosis. Even when symptoms come on insidiously, the patient is able to remember slight variations in progression. Once at their height, symptoms tend to improve or disappear. If relapses occur, they more often consist of an exacerbation of existing symptoms, than of the appearance of new ones, though both may concur.

A single isolated "signal symptom," such as numbness of one extremity, diplopia, or central scotoma, may appear and disappear long before the disease as a whole becomes recognized.

In analysis of symptoms and signs, the important points for diagnosis are evidence of lesions scattered in time and space. Most of the lesions affect white matter, so that signs of injury to the cortico-spinal, cerebellar and vestibular systems are common. The lesions are rarely complete over large areas, so that gross sensory defects are unusual (except in acute stages). Paraplegia with a sensory level is not rare, usually as a terminal event. Grey matter suffers less than white matter, so that convulsions, muscle atrophies, and nuclear palsies are unusual; but the more fulminating the onset, the less the lesions respect nerve cells.

Examination of the spinal fluid is of great help in diagnosis. In multiple sclerosis according to Merritt,³⁸ the cells are increased beyond 5 in 28 per cent of cases, but rarely over 100. Protein is increased in 24 per cent of cases. Abnormal gold sol curves are found in 71 per cent of cases. A slight increase of pressure is occasionally recorded. In only 17 per cent of cases is the fluid entirely normal. Naturally, examination of the spinal fluid is of great help in ruling out syphilis and tumor.

A somewhat different picture is found in fulminating cases of "encephalomyelitis." The cell count is usually higher, and may reach 8,000. Pressure is occasionally elevated. The protein is rarely much elevated, and a frankly positive gold sol curve is practically never found.

TABLE I
PRINCIPAL SYMPTOMS IN 133 CASES OF MULTIPLE SCLEROSIS

| | AS FIRST | SYMPTOM | AS SUBSEQUENT SYMPTOM | | |
|---------------------------|----------|----------|--------------------------|----------|--|
| | Total | Improved | Total | Improved | |
| Paraplegia | 19 | 9 | 70 | 22 | |
| Ataxia; tremor | 23 | 10 | 44 | 15 | |
| Monoplegia | 24 | 13 | 33 | 18 | |
| Scotoma . | 20 | 16 | 32 | 20 | |
| Numbness of one extremity | 20 | 15 | 26 | 13 | |
| Bladder symptoms | 6 | 4. | 39 | 15 | |
| Diplopia | 18 | 12 | 24 | 14 | |
| Numbness of both legs | 7 | 5 | 19 | 15 | |
| Disturbance of speech | 2 | 2 | 22 | 4 | |
| Mental deterioration | 2 | 0 | 16 | 1 | |
| Hemiparesis | 6 | 3 | 11 | 5 | |
| Pain (radicular) | 1 | 0 | 13 | 5 | |
| Hemianesthesia , | 5 | 4 | 4 | 4 | |

If the patient survives this acute phase, the spinal fluid picture gradually becomes that typical of multiple sclerosis.¹²

Spinal punctures (and other procedures such as encephalography or even venipuncture) are sometimes followed by exacerbations—doubtless a non-specific effect.

Visual fields should be plotted in every suspected case. The presence of a central or ceco-central scotoma, even relative, is characteristic.

Electroencephalography is sometimes useful. In cases in which only paraplegia or ataxia are evident, a cerebral focus may be revealed. Fluctuations in the extent of an area of phase reversal may be the clearest manifestation of the typical remissions and exacerbations.

A cystometrogram often furnishes additional objective evidence of a lesion of the cord.

Psychometric studies are helpful in assessing prognosis and ability to work. The record of achievement is usually spotty and variable. Course and Prognosis: The diagnosis of multiple sclerosis is usually

considered to be worse than a sentence of death. Thus, Osler's textbook states that "ultimately, the patient, if not carried off by some intercurrent infection, becomes bedridden." Certainly all of us have seen patients in the late stage of the disease, helpless and miserable, yet clinging to life often for a decade or two.

On the other hand, a survey of a large series of cases shows that remissions are common, and substantial spontaneous recovery is not rare. Von Hoesslin²⁸ found 17 per cent of remissions among his 516 cases, lasting for periods up to forty-five years. Dr. Brown and I reviewed 133 cases which we had personally observed, and found that some improvement occurred at some time in ninety-two of them. Twenty per cent were working, 47 per cent were ambulatory, 15 per cent were helpless, and 12 per cent were dead. It was clear, moreover, that certain symptoms carried in themselves a better prognosis than others. Data for the more common symptoms are given in Table I.⁷

The following conclusions resulted from the detailed study.

- 1. The prognosis is better for early symptoms than for late ones—hence, of course, the transient character of the "signal symptoms."
- 2. Symptoms evidently due to small lesions, such as diplopia, central scotoma or sensory disturbances of one extremity, tend to regress within a few months, while symptoms due to larger lesions such as paraplegia, ataxia and mental deterioration are usually permanent.
- 3. Isolated symptoms disappear in a far higher proportion of cases than do the same symptoms occurring in conjunction with others (usually therefore due to large lesions).
 - 4. Symptoms tend to grow more severe as the disease progresses.
- 5. Cases in which severe symptoms occur at the outset, usually run a much more malignant course than those in which the early symptoms are mild and transient. There are, however, many exceptions to this rule.
- 6. Cases seen in office practice tend to do much better than those seen on hospital wards. Periods of improvement were found in 87 per cent of the former and in only 62 per cent of the latter. Whether this is because ward patients have more severe symptoms at the outset, or whether it is due to differences in economic level, the fact is undoubted.

While the survey did not bring out the point clearly, it is widely believed by neurologists that the course of the demyelinating diseases is more stormy ("encephalitic") in children, more gradual in middle life. An onset after 40 is somewhat unusual, but may occur.

Etiology and Mechanism of the Disorder: All the information we can muster is still too scanty to give a complete picture of the pathogenesis of multiple sclerosis and the "encephalitides."

Some general possibilities can at once be ruled out. It is not primarily a hereditary disease. Thums³⁹ has traced 14 pairs of identical twins, of which one had multiple sclerosis; in no instance was the other affected. (This paper adds a 15th pair). There are, to be sure, occasional instances in which two cases have occurred in the same family, but they are probably to be ascribed either to coincidence, or to confusion with hereditary ataxia which sometimes closely simulates multiple sclerosis.

Multiple sclerosis and the related disorders are not deficiency diseases. They are rarest where dietary deficiencies are most prevalent—namely, in China and our own Southern states. Attempts at treatment with high vitamin diets and injections of liver extract were begun fourteen years ago at the Boston City Hospital, and were abandoned when it became clear that the course of the disease was unaffected.⁴⁰ More recently, intensive treatment with a wider variety of vitamins (including vitamin E) at the Neurological Institute has yielded equally negative results.

It is extremely unlikely that multiple sclerosis and the demyelinating "encephalitides" are due to a living virus. The pathologic changes are entirely distinct from those resulting from known specific infections; for example, poliomyelitis and equine encephalitis.⁴¹ Although countless attempts have been made to transmit the disease to animals, by many bacteriologists including Noguchi, all have been negative; not a single one of Koch's postulates have been fulfilled. The presence of spirochetes in the lesions has been occasionally reported, but competent observers have failed to corroborate the observation.⁴² Schaltenbrand's recent brief note,⁴³ reporting production of a disease in animals not resembling multiple sclerosis, is unsatisfactory in many respects.

Meanwhile, some positive evidences indicating an entirely different type of etiology have gradually accumulated. 44, 45 Lesions closely resembling those of "encephalomyelitis" in the acute stage, and those of multiple sclerosis in the chronic stage, have been produced by obstruction of cerebral venules. 45 Similar lesions may be brought about by injection of coagulants 22 or of asphyxial poisons. 25 Thrombi are found regularly in acute lesions, both of "encephalomyelitis" and of

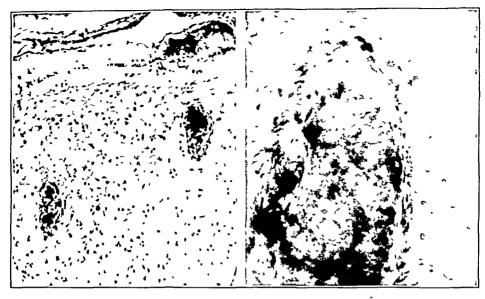
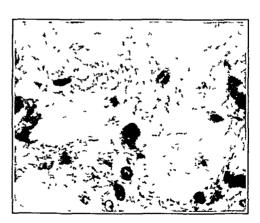


Fig. 3 Fig. 4

Fig. 3-Multiple sclerosis, with death in an acute exacerbation. Two small thrombosed veins draining a plaque. Mallory's connective tissue stain.

Fig 4—Multiple sclerosis Fresh thrombus in a vein adjacent to a plaque, Mallory's connective tissue stain

Fig. 5—Multiple sclerosis Fibrous cords representing the remnants of obstructed vessels, adjacent to the lateral ventricle. Mallory's connective tissue stain



multiple sclerosis (Figures 3, 4, 5) and in other organs of the body.⁴⁴ There is a peculiar lability of the clotting mechanism in cases of multiple sclerosis.^{46,47}

All these facts may be fitted together in some such theory as the following: There are individuals who suffer from a peculiar lability of the clotting mechanism of the blood. Whether this is congenital or acquired is not clear. If it exists, however, any slight disturbance of

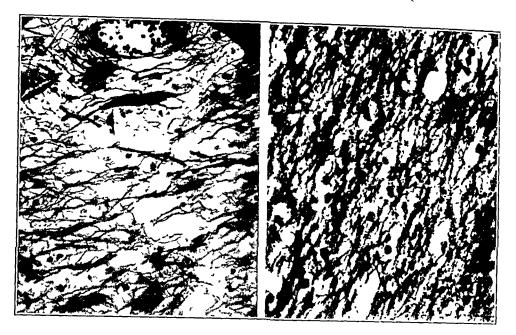


Fig. 6-Multiple sclerosis. Axis cylinders within a plaque (left), and in relatively normal adjacent tissue (right).

the equilibrium of the body may precipitate a shower of minute thrombi in various tissues. Most of these cause no permanent damage, but any that occur in the brain leave a permanent landmark behind and a local vascular abnormality which predisposes to further clotting. If the process is sufficiently stormy, a widespread destruction is produced, and the patient dies with the manifestations of "encephalomyelitis." Limitations of space forbid going into further details, but they may be found in some of the references already cited.

Treatment: A study of the lesions of multiple sclerosis makes it clear that a large proportion of axis cylinders are destroyed in the acute phase of the process⁴⁸ (Figure 6). The larger the lesion, and the longer the disease has continued, the more severe the damage to axons. A useful regeneration of axis cylinders in the central nervous system is at present inconceivable. It follows, therefore, that no treatment (beyond ordinary regulation of hygiene) can be expected to influence the course of lesions which have already occurred.

This conclusion is borne out by a statistical study of the effects of the various forms of treatment now in use.⁴⁰ The average rate of improvement closely approximates that found in untreated cases.

These facts, and the theory of pathogenesis just outlined, do not necessarily mean that all attempts at treatment are hopeless. They do, however, imply, that a given treatment should be judged not on the basis of its effect on existing symptoms, but on its success in preventing relapses. If exacerbations can be definitely prevented, the normal tendency is to recovery.

This goal does not seem permanently out of reach. There are several steps toward it which are always worth considering.

In the first place, possible precipitating causes should be avoided when possible. A search should be made for focal infections. The patient should be protected against over-exertion and accidents, as far as possible. Female patients should avoid pregnancy.

In the second place, advantage should be taken of the regional differences in incidence of the disorder when circumstances permit. Life in a warm, dry climate seems to have a beneficial effect on many cases possibly because the common infections of the nose and throat are less prevalent there. Unfortunately, this form of treatment is out of the reach of most patients.

In the third place, a constant search should be made for means of correcting the instability of the plasma. The use of anticoagulants naturally suggests itself; and actually they can be shown to have an effect on some experimental forms of the disease.²² None of the anticoagulants given by vein (for example, heparin) seem promising. Cysteine is a feeble anticoagulant,⁴⁹ which has seemed to afford some protection to some patients. By far the most promising substance seems to be dicoumarin,⁵⁰ and it is now being tried on a series of cases.

Meanwhile, symptomatic treatment should not be forgotten. The patient's health and strength must be maintained in every possible way. If spasticity is annoying, small doses of bromides are sometimes useful. Alcohol in moderation may help the patient's spirits, and paradoxically, his balance if ataxia and tremor are present. The use of sandalwood oil and of tincture of belladonna is often helpful in cases of urgency. An important point is that the urgency will often pass off if the patient makes up his mind to disregard it or distracts his attention to some other task. In cases in which the bladder disturbances are of long standing or accompanied by infection, periods of tidal irrigation⁵¹ are often extremely helpful. Patients with hemiataxia may learn to avoid staggering by habitually leaning toward the more normal side. The disagreeable

sensation of slapping the ground with the toes which is a common component of the spastic gait may often be mitigated by practice in placing the heel on the ground first, then rolling the weight along the outer edge of the foot to the toe. A brace may be worn for toe-drop. Subarachnoid alcohol injection or root section may be needed for radicular pains or for contractures in bedridden patients. The foot placement exercises so useful in tabes, are often of benefit in multiple sclerosis also. Special telescopic lenses are available for patients whose loss of vision is relatively fixed and constitutes the most disabling symptom. Motorized wheel chairs may be of use for those unable to walk.

CONCLUSION

Multiple sclerosis is often regarded as a "rare and mysterious disease." It is certainly not rare, and it is much less mysterious than it once was. A careful, patient analysis of the remaining problems, step by step, gives promise of revealing the roots of the disorder. Even with what we know already, the directions which a rational system of treatment should take is already fairly clear.

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THE MANAGEMENT OF HYPERTENSION*

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two periods; an empirical period during which treatment consisted of administration of vasodilator and other hypotensive drugs and a second period, which brings us up to date, during which treatment presumes to be based upon knowledge of the causative mechanism.

During the period of empiricism, drugs have varied from the evanescent vasodilator nitrites through the ineffectual extracts of watermelon seeds and garlic up to the dangerous thiocyanate. These forms of therapy have had little effect on the individual sufferer and no effect on the incidence of hypertensive disease; nor was any significant addition made to the understanding of the underlying mechanism of essential hypertension. Because of the recent revival of interest in thiocyanate I will review our experience.

In 1932 Dr. Chasis and I^{1,2} studied the effect of thiocyanate in hypertension on the wards of the Third Medical Division of Bellevue Hospital, and the Nephritis and Hypertension Division of the New York University Medical College Clinic.

Tables I and II give a summary of the results of treatment in an ambulatory and a hospitalized group of patients with essential hypertension. There were forty-four trials in the ambulatory group and twenty-five trials in the hospital group. The ages ranged from 29 to 65 years. The period of control in the ambulatory group ranged from 7 to 378 days and in the hospital group from 5 to 105 days. It will be noted that a "trial" was considered effective when the blood pressure fell to. or below, 165 systolic and 100 diastolic, arbitrarily chosen as our criterion. There are instances (see cases 20, 24 and 41, Table I, and cases 11, 14 and 15, Table II) in which marked falls in both systolic and diastolic pressure occurred, but the blood pressure remained distinctly

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TABLE I
RESULTS OF TREATMENT WITH THIOCYANATE IN
ESSENTIAL HYPERTENSION: AMBULATORY GROUP

| No. | Age | Blood Pressure | Average, | Control Period, | Lowest Blood Pressure after Treat- ment | Thio- cyanate Intoxi- cation | Effective in Lowering Blood Pressure |
|--------|----------|--|--------------------|--------------------|---|---------------------------------------|--------------------------------------|
| | { } | $Mm.\ Hg$ | Mm.Hg | Days | ment | | |
| | 54 | 220/110 to 198/104 | 213/107 | 126 | 150/85 | No | Yes |
| 1 2 | 54 54 | 220/110 to 190/104 220/110 to 190/104 | 190/104 | 161 | 165/ 90 | No | Yes |
| 3 | 64 | 220/120 to 185/100 | 205/109 | 35 | 140/ 70 | No | Yes |
| 4 | 65 | 230/138 to 175/104 | 203/116 | 294 | 190/ 92 | Yes | No |
| 5 | 46 | 260/130 to 210/110 | 252/120 | 378 | 185/ 95 | No | No |
| 6 | 56 | 205/120 to 170/ 98 | 180/105 | 231 | 135/ 70 | Yes | Yes |
| 7 | 37 | 240/140 to 188/106 | 203/122 | 273 | 158/ 95 | No | Yes |
| 8 | 53 | 236/156 to 198/120 | 220/136 | 182 | 157/ 90 | No | Yes |
| 9 | 53 | 215/125 to 175/115 | 196/117 | 35 | 150/ 75 | No | Yes |
| 10 | 53 | 205/120 to 174/105 | 190/113 | 14 | 145/ 90 | No | Yes |
| 11 | 29 | 268/132 to 180/132 | 206/132 | 133 | 180/125 | No | No |
| 12 | 29 | 268/132 to 180/132 | 198/132 | 168 | 185/125 | Yes | No |
| 13 | 29 | 268/132 to 180/132 | 190/130 | 203 | 150/110 | No | No |
| 14 | 50 | 210/120 to 160/108 | 174/112 | 33 | 155/ 95 | No | No |
| 15 | 42 | 260/160 to 132/ 80 | 187/122 | 53 | 207/127 | No | No |
| 16 | 38 | 182/145 to 168/135 | 177/140 | j 14 | 180/125 | No | No |
| 17 | 58 | 212/122 to 196/109 | 203/116 | 84 | 165/105 | No | No |
| 18 | 61 | 224/130 to 198/110 | 210/119 | 35 | 192/105 | No | No Yes |
| 19 | 62 | 240/125 to 200/ 96 | 217/109 | 91 | 158/ 90 | No | No |
| 20 | 51 | 222/142 to 216/140 | 218/141 | 28 | 184/112 | No | No |
| 21 | 46 | 250/118 to 195/100 | 222/109 | 62 | 184/ 90 | No No | Yes |
| 22 | 64 | 210/ 88 to 190/ 88 | 198/ 88 | 32 | 150/ 75 | No | No |
| 23 | 53 | 230/125 to 170/110 | 206/121 | 48 | 170/ 98 | No | No |
| 24 | 40 | 250/130 to 232/120 | 239/123 | 42 | 186/106 | No | No |
| 25 | 46 | 225/110 to 184/ 96 | 209/103 | 84 | 190/100 | No | No |
| 26 | 62 | 206/100 to 188/ 92 | 200/ 96 | 28 | 164/82 | No | No |
| 27 | 65 | 212/110 to 160/ 90 | 186/101 | 111 | 178/ 94 | No | No |
| 28 | 54 | 212/104 to 198/ 94 | 206/ 97 | 42 | 170/ 90 174/ 96 | No | No |
| 29 | 45 | 200/128 to 185/102 | 192/115 | 56 | 188/108 | No | No |
| 30 | 54 | 210/118 to 165/100 | 182/100 | 133 | 178/110 | No | No |
| 31 | 42 | 199/125 to 190/108 | 196/116 | 21 | 164/120 | No | No |
| 32 | 51 | 250/158 to 184/110 | 243/129 | 203 | 156/ 96 | No | No |
| 33 | 55 | 250/140 to 180/ 98 | 200/110 | 28 | 215/110 | No | No |
| 34 | 62 | 235/130 to 180/115 | 208/123 | 469 | 166/ 90 | No | No |
| 35 | 46 | 260/130 to 185/ 92 | 215/110 | ۱ | 150/ 72 | No | No |
| 36 | 64 | 215/120 to 160/180 | 200/105 | | 190/ 90 | No | No |
| ′ 37 | 63 | 230/138 to 175/ 95 | 205/110 | | 175/108 | No | No |
| 38 | 54 | 220/120 to 165/100 | 195/105 | | 176/110 | No | No |
| 39 | 46 | 250/118 to 170/ 94 | 185/102 | ? | 142/ 70 | No | Yes |
| 40 | 64 | 216/ 96 to 184/ 78 | 199/ 88 215/124 | | 182/100 | No | No No |
| 41 | 50 | 218/126 to 212/122 | | | 200/112 | No | No No |
| 42 | 53 | 220/120 to 170/ 98 | | | 186/104 | No | No |
| 43 | 40 | 234/128 to 186/106 | | | 190/90 | Yes | 1 110 |
| 44 | | 230/125 to 180/100 | 200/110 | 1 | | | |

TABLE II
RESULTS OF TREATMENT WITH THIOCYANATE IN ESSENTIAL HYPERTENSION: HOSPITALIZED GROUP

| | | Blood Pressure | Control | Control | Lowest Blood Pressure after | Thio- cyanate Intoxi- | Effective in Lowering |
|---|-------|--------------------|----------|---------|-----------------------------|-----------------------------|-----------------------------|
| No. | Age | Range, | Average, | Period, | Treat- | cation | $_Blood$ |
| • | 22,70 | Mm.Hg | Mm.Hg | Days | ment | (| Pressure |
| | | | ···· | | | | · |
| 1 | 50 | 210/120 to 160/108 | 174/112 | 15 | 160/100 | No | No |
| 2 | 53 | 232/131 to 198/125 | 209/129 | 8 | 129/ 70 | No | Yes |
| 3 | 46 | 208/120 to 190/108 | 194/114 | 35 | 170/110 | No | No |
| 4 | 57 | 230/130 to 186/ 92 | 202/113 | 11 | 118/ 90 | Yes | Yes |
| 5 | 53 | 236/131 to 196/120 | 220/113 | 16 | 146/ 74 | No | Yes |
| 6 | 53 | 230/130 to 220/106 | 224/113 | 7 | 210/120 | Yes | No |
| 7 | 55 | 180/105 to 158/ 95 | 174/102 | 12 | 115/80 | No | Yes |
| 8 | 56 | 220/130 to 190/100 | 207/110 | 8 | 158/ 90 | Yes | Died* |
| 9 | 40 | 225/130 to 201/100 | 237/112 | 13 | 204/ SS | Yes | Died* |
| 10 | 63 | 210/146 to 190/128 | 202/133 | 5 | 140/80 | Yes | Yes |
| 11 | 50 | 250/155 to 216/120 | 230/130 | 18 | 180/100 | No | No |
| 12 | 50 | 230/130 to 186/100 | 205/110 | 47 | 190/120 | Yes | No |
| 13 | 63 | 240/168 to 190/128 | 215/145 | 31 | 138/ 70 | No | Yes |
| 14 | 52 | 228/138 to 208/104 | 221/122 | 8 | 182/ 90 | No | No |
| 15 | 55 | 250/140 to 198/120 | 227/137 | 12 | 180/100 | No | No |
| 16 | 55 | 250/140 to 180/ 98 | 200/110 | 105 | 210/114 | Yes | No |
| 17 | 49 | 260/140 to 190/ 96 | 204/114 | 25 | 180/ 98 | No | No |
| 18 | 43 | 198/132 to 170/112 | 181/126 | 14 | 148/86 | No | Yes |
| 19 | 46 | 200/100 to 185/ 95 | 187/109 | 36 | 162/ 92 | No | No |
| 20 | 48 | 208/118 to 178/108 | 195/115 | 13 | 186/ 98 | No | No |
| 21 | 44 | 168/114 to 154/ 92 | 159/103 | 9 | 162/ 90 | Yes | No |
| 22 | 51 | 261/132 to 210/120 | 253/128 | 9 | 164/84 | Yes | Yes |
| 23 | 51 | 182/120 to 162/ 98 | 173/ 98 | 19 | 140/ 88 | No | No |
| 21 | 48 | 198/160 to 184/ 98 | 200/119 | 17 | 184/ 96 | No | No |
| 25 | 51 | 250/138 to 192/118 | 221/124 | 11 | 196/110 | No | No |

^{*}Death was due to thiocyanate intoxication.

above 165 systolic and 100 diastolic. In order to adhere to our strict standard of criteria for effect, all these instances, because of the difficulty of their interpretation, were considered ineffective. Table III shows the effect of thiocyanate on the hypertension of chronic diffuse glomerulonephritis. In this group, care was taken not to include patients during an acute exacerbation because of the possibility of an accompanying spontaneous fall of blood pressure as the acute condition subsided.

Table IV represents follow-up observations on fourteen patients in whom the blood pressure was effectively lowered by thiocyanate, and the duration of the hypotensive effect after discontinuance of the drug. The hypotensive effect in this group of patients persisted for from 7 to

| Table III |
|--|
| RESULTS OF TREATMENT WITH THIOCYANATE IN NEPHRITIC |
| (CHRONIC DIFFUSE GLOMERULONEPHRITIS) HYPERTENSION |

| No. | Age | Blood Pressure Range, Mm. Hg | Control Average, Mm. Hg | Control Period, Days | Lowest Blood Pressure after Treatment | Thio- cyanate Intoxi- cation | Effective in Lowering Blood Pressure |
|-----------------------|----------------------------|--|---|----------------------------|--|---------------------------------------|--------------------------------------|
| 1 2 3 4 5 | 21 44 47 60 60 | 220/140 to 180/120 290/180 to 234/156 248/160 to 202/125 210/110 to 176/ 90 210/110 to 176/ 90 | 196/130 290/165 229/141 195/ 98 195/ 95 | 7 9 8 150 143 | 114/ 64 138/ 95. 160/100 194/ 86 170/ 86 | No No No No No | Yes Yes Yes Yes No No |

to, its control level. There seemed to be no constant relationship between the persistence of the artificially lowered blood pressure and the amount of thiocyanate required to produce the lowering.

Table V indicates that the effect of thiocyanate cannot be logically anticipated from the average daily dose or the duration of medication. It will be seen that a "trial" was considered completed when the blood pressure fell in accordance with our stated criterion; when toxic symptoms occurred; or when the total amount of thiocyanate administered was in most instances distinctly greater than the amount usually recommended by others as therapeutically effective.

In Table VI, the data of the preceding table are condensed and summarized. They represent an evaluation of the clinical usefulness of various dosages of thiocyanate. The absence of therapeutic effect with 0.163 gm. (2½ grains) daily administered from 77 to 148 days in four patients seemed sufficient reason for considering it an ineffective dosage. The great frequency of toxic manifestations with from 0.978 to 1.62 gm. (from 15 to 25 grains) given daily in ten trials was sufficient evidence for considering this dosage harmful. The dosage of from 0.489 to 0.815 gm. daily (from 7½ to 12½ grains) was accompanied by toxic manifestations in the same percentage as it produced satisfactory lowering of the blood pressure. Moreover, two fatalities occurred in this group as a result of thiocyanate poisoning. The highest percentage of effectiveness with the lowest incidence of toxicity was observed in those patients who received 0.326 gm. (5 grains) daily.

| TABLE IV | | | | | |
|---------------|----|-------------|--------|----|-------------|
| PERSISTENCE (| OF | HYPOTENSIVE | EFFECT | OF | THIOCYANATE |

| Number Ambulatory group | Type of Hypertension | Average Daily Dose, Gm. | Total Dose, Gm. | Per- sistence, Days |
|----------------------------|---|----------------------------------|-------------------------------|---------------------------|
| 1 | Essential Essential Essential Essential Essential Essential Essential Essential | 0.326 | 8.48 | 28 |
| 2 | | 0.326 | 10.76 | 26 |
| 3 | | 0.652 | 13.69 | 49 |
| 4 | | 0.326 | 15.98 | 34 |
| | | 0.326 | 29.35 | 110 |
| 5 | | 0.489 | 31.96 | 55 |
| 6 | | 0.326 | 33.66 | 48+ |
| 7 | | 0.489 | 75.50 | 41 |
| 9 10 11 12 | Essential Essential Nephritic Nephritic | 0.326 0.652 0.652 0.978 | 4 56 8.48 9.29 10.43 | 28+ 15+ 14 73+ |
| 13 | Essential | 1.192 | 26 35 | 7 |
| 14 | Essential | 0.613 | 31.14 | 32 |

The data in Table VII indicate the relative excretion rate of thiocyanate in patients with essential hypertension and in patients with the hypertension of chronic diffuse glomerulonephritis. Furthermore, when the same amount of thiocyanate was administered in a single dose to a "normal" person and one with chronic diffuse glomerulonephritis, the "normal" person excreted an average daily amount twice as great as did the patient with nephritis. It would seem from these observations that the ease with which thiocyanate is excreted bears a direct relationship to the functional integrity of the kidney. Likewise, there appears to be a distinct lack of relationship between the average amount excreted per day and the average amount administered per day. The slow excretion rate of thiocyanate in the presence of glomerulonephritis is reflected in the prolongation of its time for complete excretion as compared with a "normal" person. This is shown in Table VIII. The remaining data in this same table clearly indicate that the days necessary for complete excretion of the drug are roughly proportional to the total amount administered. The observation that at least 4 days are necessary for the complete excretion of a single dose as small as 0.163 gm. (2½ grains), in persons with normal renal function, is striking evidence of the great ease with which thiocyanate accumulates in the body on continuous administration over a period of time.

TABLE V

RELATION OF THE DOSAGE OF THIOCYANATE TO THE EFFECT ON BLOOD PRESSURE AND THE OCCURRENCE OF TOXIC MANIFESTATIONS

| === | | | | | | |
|-----|--------------------------|--|----------------------------------|---|-----------------------|------------------|
| No. | $Type\ of\ Hypertension$ | Blood Pressure Lowered to or Below 165/100, mm. Hg. | Average Daily Dose, Gm. | Duration of Medi- cation, Days | Total Dose, Gm. | Toxic Effect |
| 1 | Essential | Yes | 0.326 | 14 | 4.56 | No |
| 2 | Essential | Yes | 0.652 | 7 | 4.56 | No |
| 3 | Essential | Yes | 0.326 | 14 | 4.56 | No |
| 4 | Essential | No | 0.326 | 18 | 5.87 | No |
| 5 | Essential | No | 0.652 | 9 | 5.87 | Psychosis |
| 6 | Essential | No | 0.978 | 7 | 6.85 | No |
| 7 | Essential | No | 0.326 | 25 | 8.15 | No |
| 8 | Essential | No | 0.815 | 10 | 8.15 | Nausea, vomiting |
| 9 | Essential | Yes | 0.326 | 27 | 8.80 | No |
| 10 | Essential | No | 0.226 | 28 | 9.13 | No |
| 11 | Essential | No | 0.652 | 14 | 9.13 | No |
| 12 | Essential | Yes | 0.326 | 28 | 9.13 | Psychosis |
| 13 | Essential | Yes | 0.978 | 10 | 9.78 | No |
| 14 | Essential | No | 0.652 | 15 | 9.78 | Death* |
| 15 | Essential | No | 0 326 | 33 | 10.76 | No |
| 16 | Essential | No | 0.405 | 28 | 11.34 | Fatigue |
| 17 | Essential | No | 1.620 | 7 | 11.34 | Psychosis |
| 18 | Essential | Yes | 0.326 | 35 | 11.41 | No |
| 19 | Essential | No | 0.326 | 35 | 11.41 | No |
| 20 | Essential | No | 0.326 | 35 | 11.41 | No |
| 21 | Essential | No | 0.170 | 69 | 11.73 | Dermatitis |
| 22 | Essential | No | 0.978 | 12 | 11.74 | No |
| 23 | Essential | No | 0.978 | 12 | 11.74 | No |
| 24 | Essential | No | 0.163 | 77 | 12.55 | No |
| 25 | Essential | No | 0.978 | 13 | 12.71 | Psychosis |
| 26 | Essential | No | 0.326 | 40 | 13.04 | No |
| 27 | Essential | No | 0.652 | 20 | 13.04 | No |
| 28 | Essential | No | 0.326 | 40 | 13.04 | No |
| 29 | Essential | Yes | 0.691 | 19 | 13.13 | No |
| 30 | Essential | No | 0.326 | 42 | 13.69 | No No |
| 31 | Essential | Yes | 0.652 | 21 | 13.69 | No No |
| 32 | Essential | No | 0.326 | 42 | 13.69 | |
| 33 | Essential | No | 0.326 | 42 | 13.69 14.01 | Fatigue, nausea |
| 34 | Essential | Yes | 0.326 | 43 | 14.49 | |
| 35 | Essential | Yes | 0.805 | 18 | 15.97 | |
| 36 | Essential | No | 0.326 | 49 | 15.97 | |
| 37 | Essential | Yes | 0.326 | 49 35 | 17.11 | |
| 38 | | No | 0.489 | 55 | 17.93 | |
| 39 | | No | 0.326 | 28 | 18.26 | |
| 40 | | No | 0.652 | 28 | 18.26 | |
| 41 | 1 | No | 0.652 | 121 | 19.72 | |
| 42 | 1 | No | 0.163 | 63 | 20.54 | |
| 43 | Essential | No | 0 326 | 66 | 21.51 | |
| 44 | Essential | Yes | 0.326 | 69 | 22.49 | |
| 45 | Essential | Yes | 0 326 | 70 | 22.82 | No No |
| 46 | Essential | Yes | | 71 | 23.15 | |
| 47 | Essential | No | 0.326 | 148 | 24.12 | No |
| 48 | l •• 1 | No | 0.108 | | 1 | 1 |
| | 1 | | | 0001 | , | |

[Continued on p. 323]

Table V-(Continued)

| No. | Type of Hypertension | Blood Pressure Lowered to or Below 165/100, mm. Hg. | Average Daily Dose, Gm. | Duration of Medi- cation, Days | Total Dose, Gm. | Toxic Effect |
|------------|-------------------------|--|----------------------------------|---|-----------------------|--------------|
| 49 | Essential | No | 0.326 | 75 | 24.45 | No |
| 50 | Essential | No | 0.326 | 77 | 25.10 | No |
| 51 | Essential | No | 0.326 | 77 | 25.10 | No |
| 52 | Essential | Yes | 0.326 | 78 | 25.42 | N_0 |
| 53 | Essential | No | 0.489 | 52 | 25.43 | N_0 |
| 54 | Essential | No | 0.648 | 41 | 26.57 | No |
| 55 | Essential | Yes | 1.210 | 22 | 26.62 | Psychosis |
| 56 | Essential | No | 0.652 | 41 | 26.73 | N_0 |
| 57 | Essential | No | 0.652 | 42 | 27.38 | N_{0} |
| 58 | Essential | No | 0.326 | 84 | 27.38 | N_0 |
| 5 9 | Essential | No | 0.652 | 42 | 27.38 | N_{0} |
| 60 | Essential | No | 0.652 | 49 | 31.95 | No |
| 61 | Essential | Yes | 0.638 | 51 | 32.54 | Psychosis |
| 62 | Essential | No | 0.652 | 50 | 32.60 | No |
| 63 | Essential | Yes | 0 978 | 35 | 34.27 | No |
| 64 | Essential | Yes | 0.652 | 55 | 35.86 | No |
| 65 | Essential | No | 0.652 | 55 | 35.86 | N_0 |
| 66 | Essential | No | 0.578 | 78 | 45.08 | N_0 |
| 67 | Essential | No | 0.652 | 74 | 48.25 | No |
| 68 | Essential | No | 0.652 | 100 | 65.20 | N_0 |
| 69 | Essential | No | 0.326 | 203 | 66.18 | No |
| 70 | Glomerulonephritis | Yes | 0.326 | 19 | 6.19 | N_0 |
| 71 | Glomerulonephritis | Yes | 0.978 | 10 | 9.78 | N_0 |
| 72 | Glomerulonephritis | Yes | 1.080 | 10 | 10.80 | No |
| 73 | Glomerulonephritis | No | 0.326 | 64 | 20.86 | No |
| 74 | Glomerulonephritis | No | 0.652 | 76 | 49.55 | No |
| 1 | Normal blood pressure | Yes** | 0.652 | 5 | 3.26 | No |
| 2 | Normal blood pressure | Yes** | 0.326 | 14 | 4.56 | No |
| 3 | Normal blood pressure | Yes** | 0.978 | 5 | 4.89 | No |
| 4 | Normal blood pressure | Yes** | 0 326 | 36 | 11.74 | No |

* Death due to thiocyanate intoxication.

Table IX is a summary of the results of thiocyanate administration in the entire group studied. The blood pressure was effectively lowered in 31 per cent of the hypertensive subjects studied. Almost invariably, a fall in blood pressure was accompanied by subjective improvement. However, subjective improvement occurred in many patients on thiocyanate therapy in whom no lowering of blood pressure occurred. This led us to believe that such improvement was largely psychic.

Furthermore, there is no constant dosage at which either a toxic or a therapeutic effect may be anticipated. Some of the inconstancies

^{**} The fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days.

| | | TABLE | VI | | | |
|---------------|----|-------------|------|---------|-------|---------|
| EFFECTIVENESS | OF | THIOCYANATE | WITH | VARIOUS | DAILY | DOSAGES |

| Daily Dose, Gm. | Number of Trials | Blood Pressure Lowered to or Below 165/100 mm. Hg. | Effec- tiveness, Per Cent | Number of Toxic Cases | Thio- cyanate Intoxi- cation, Per Cent | Number of Fatal Cases Due to Thio- cyanate Intoxi- cation |
|-------------------------------|------------------------|---|---------------------------------|--------------------------------|--|---|
| 0.163 (2½ grains) | 4 | 0 | o | 1* | 25 | 0 |
| 0.326 (5 grains) | 34 | 12 | 35.2 | 3 | 8.8 | 0 |
| 0.489-0.815 (7.5-12.5 grains) | 26 | 6 | 23 | 6 | 23 | 2 |
| 0.978-1.63 (15-25 grains) | 19 | 5 | 50 | 3 | 33,3 | 0 |

^{*} Maculopapular dermatitis.

TABLE VII

A COMPARISON OF THE EXCRETION RATE OF THIOCYANATE IN
ESSENTIAL HYPERTENSION AND NEPHRITIC HYPERTENSION*

| No. | Type of Hypertension | Average Daily Dose, Gm. | Average Thiocy- anate Excretion, Gm. per 24 Hr. |
|-----|----------------------|---|---|
| 1 | Nephritic | 0.978 | 0.097 |
| 2 | Nephritic | 1.004 | 0.277 |
| 3 | Nephritic | 0.652 | 0.250 |
| 4 | Essential | 0,978 | 0 540 |
| 5 | Essential | 0.915 | 0.557 |
| 1 2 | Normal Nephritic | 1.143 (single dose) 1.143 (single dose) | 0 088 0.043 |

^{*} Chronic diffuse glomerulonephritis.

observed are illustrated by the following observations: One patient who responded, by a fall in blood pressure, to 0.326 gm. (5 grains) daily on three successive occasions failed subsequently to respond to a repetition of treatment with the same dosage over a similar period of time. Another patient who responded, by a satisfactory fall in blood pressure, to 0.326 gm. (5 grains) given daily on two different occasions failed subsequently to respond to 0.652 gm. (10 grains) daily given over a

TABLE VIII

EXCRETION TIME OF THIOCYANATE (SINGLE DOSE)

| Diagnosis | One Dose, Gm. | Days Necessary for Complete Excretion | | |
|-------------|---------------|---------------------------------------|--|--|
| Normal* | 0.163 | 5 | | |
| Normal | 0.163 | 4 . | | |
| Normal | 0.163 | 4 , | | |
| Normal | 0.163 | 4 | | |
| Normal | 0.326 | 9 | | |
| Normal | 0.652 | 11 | | |
| Normal | 1.143 | 14 | | |
| Nephritis** | 1 143 | 22 | | |

^{*} No evidence of organic disease.

TABLE IX
SUMMARY OF RESULTS OF TREATMENT WITH THIOCYANATE

| | Number of Trials | Blood Pressure Lowered to or Below 165/100, mm. Hg. | Effectiveness in Lowering Blood Pressure, Per Cent | Toxic | Deaths Duc to Thiocya- nate Intoxi- cation |
|------------------------|------------------------|---|--|-------|---|
| Normal | 4 | 1 | 100 | 0 | 0 |
| Essential hypertension | 69 | 20 | 28 9 | 13 | 2 |
| Nephritic hypertension | 5 | 3 | 60 | 0 | 0 |
| Hypertension, total | 71 | 23 | 31 | 13 | 2 |

comparable period of time. A third patient who responded satisfactorily after a total dose of 13.2 gm. (202 grains) subsequently became severely toxic (hallucinations of sight and hearing, disorientation, etc.) on a total dose of 12.74 gm. (195 grains).

This uncertainty regarding proper dosage, coupled with the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effects, lead us to believe that thiocyanate has no place in the rational treatment of hypertension.

^{**} Chronic diffuse glomerulonephritis.

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TABLE X

AMOUNT OF THIOCYANATE IN THE BODY AT THE TIME OF THE FIRST DEFINITE FALL IN BLOOD PRESSURE AND AT THE TIME OF THE FIRST SIGN OF INTOXICATION

| | Dosage, Gm. | | Residual Drug at | Residual Drug at | Average Daily |
|------------------------|-------------|------------------|---|---------------------|----------------------------------|
| | Total | Average Daily | First Fall in Blood Pres- sure, Gm. | | Thiocyanate Output in Urine, Gm. |
| Nephritic* . | 9.78 | 0.978 | 8.96 | | 0.097 |
| Nephritic* . | 10.80 | 1.080 | 9.03 | | 0.275 |
| Essential hypertension | 9.78 | 0.652 | | 8.49 (died) | 0 086 |
| Essential hypertension | 12.71 | 0.978 | | 5.00 | 0.536 |
| Essential hypertension | 8.15 | 0,815 | | 5.73 | 0.213 |
| Essential hypertension | 9.78 | 0.978 | 8.09 | | 0.192 |
| Essential hypertension | 5.87 | 0.652 | | 3.22 | 0.151 |
| Essential hypertension | 26,62 | 1.210 | 20.88 | 21.56 | 0.262 |
| Normal | 4.89 | 0.978 | 2.29 | | 0.339 |
| Normal | 4.56 | 0.326 | 2.89 | | |
| Normal | 3.26 | 0.652 | 2.90 | | 0,115 |

^{*} Associated with diffuse glomerulonephritis.

TABLE XI
FREQUENCY OF OCCURRENCE OF TOXIC MANIFESTATIONS
IN 74 SUBJECTS

| ric Manifestations | Frequency o Occurrence |
|-------------------------------------|---------------------------|
| | 8 |
| Nausea | . 7 |
| Muscular fatigue | . 7 |
| Vomiting . | . 7 |
| Mental confusion and disorientation | . 6 |
| | . 3 |
| Motor aphasia | . 2 |
| Death | 1 |
| Dermatitis | |

This attitude was widely accepted and thiocyanate therapy in hypertension was almost completely abandoned. However, there has been a recent revival of interest principally based upon studies by Barker.³ He has indicated that repeated estimations of the blood thiocyanate concentration would serve to prevent overdosage, i.e., if the blood concentration were maintained between 6 and 12 mg. per cent, toxic effects were not likely to occur. In his series of forty-five patients no toxic effects appeared in those subjects whose blood concentration of thiocyanate was 15 mg. per cent or less.

Dr. Chasis and I had previously considered the relationship between dosage and toxic effects. However, instead of blood concentration we determined the residual drug in the body each day by subtracting the amount excreted from the amount administered. By this means we were in a position to know how much thiocyanate was retained in all body tissues and not only that in the circulating blood. Moreover, the estimation of residual drug is not subject to the fluctuation inherent in estimations of blood concentration which is in part influenced by variations in total circulating volume.

In order to determine the relationship, if any, between residual drug and the first evidence of its so-called therapeutic or toxic effect, a group was selected for study consisting of three persons with normal blood pressure, six with essential hypertension and two with hypertension associated with chronic diffuse glomerulonephritis. The results of these observations are shown in Table X. There can be little doubt from the observations presented that toxic effects and even a fatal outcome may occur in some patients who have in their tissues a smaller amount of thiocyanate than others who, not only do not become toxic, but experience a satisfactory fall in blood pressure.

Of the fifty patients with hypertension in this series treated seventy-four different times with thiocyanate, thirteen presented toxic manifestations. In eleven of these the toxic manifestations disappeared within a few hours to 4 days after discontinuance of the drug. The usual order in which the toxic symptoms made their appearance was as follows: muscular fatigue accompanied or followed by nausea; vomiting; disorientation and mental confusion; motor aphasia; hallucinations of sight and hearing; and, in the fatal cases, progression to delirium, convulsive twitchings, coma and death. The frequency with which these toxic manifestations were observed is shown in Table XI. It is noteworthy

that while ambulatory patients who become toxic notice muscle fatigue as the first indication, this symptom may pass entirely unnoticed in patients confined to bed, in whom it is not unusual for motor aphasia, mental confusion or even hallucinations to be the first sign of thiocyanate intoxication.

The remaining two patients who became toxic died of thiocyanate poisoning.

The first fatal case was that of a patient M., aged 40. Her hypertension was of the essential type. The duration of her hypertension was not known. Three months before admission to the hospital she developed a severe occipital headache, which was continuous, and dimness of vision. Her blood pressure during the control period, ranged between 255 systolic and 130 diastolic and 204 systolic and 100 diastolic. The fundi showed the changes of malignant hypertensive neuroretinitis. The concentration test showed a fixation of specific gravity between 1.008 and 1.014. The red blood cells numbered 4,000,000 and the hemoglobin content was 50 per cent. The urine was negative for albumin and blood. On the thirteenth day after admission thiocyanate was begun in dosage of 0.652 gm. daily. On the fourteenth day, after 9.12 gm. had been given, the patient complained of nausea and the blood pressure was 186 systolic and 96 diastolic. On the following day nausea was more marked, but the blood pressure had risen to 220 systolic and 110 diastolic, so that another dose of 0.652 gm. was given. Later on in this day she became somewhat confused and incoherent. Thiocyanate was discontinued. A total of 9.77 gm. had been given in 15 days. The blood pressure continued high, and on the following day she became violently delirious with hallucinations of sight and hearing, extreme motor restlessness, nystagmus and frequent convulsive movements of the extremities. She was completely disorientated, continually muttering and thrashing about so violently as to require mechanical restraint. During the last 24 hours she voided almost no urine and was markedly dehydrated in spite of repeated saline hypodermoclyses and dextrose infusions. The stuporous state became more profound, and death occurred 66 hours after thiocyanate had been discontinued. On the day of death, the blood pressure was 212 systolic and 106 diastolic. Seven days before the end the nonprotein nitrogen content of the blood was 33 mg. per hundred cubic centimeters. Two days before the end the nonprotein nitrogen content was still within the normal range, being 45 mg., and the creatin-

| Tissue | Estimation of Thiocyanate Content of Tissues of a Patient in Whom the Drug Proved Fatal,* Mg. per 100 Cc. | Estimation of Thiocyanate Content of Tissues of a Patient to Whom no Thio- cyanate was Given, Mg. per 100 Cc. |
|--------|---|---|
| Heart | 9.7 | |
| Kidney | 15.4 | Trace |
| Spleen | 9.2 | Trace |
| Liver | 14.5 | 4.0 |
| Lung | 17.0 | None |
| Bone | None | None |
| Brain | 8.0 | None |

TABLE XII

ANALYSIS OF TISSUES FOR THIOCYANATE CONTENT

ine 2.4 mg. per hundred cubic centimeters. On the same day the urea clearance showed 41.2 per cent of normal function for the first hour and 34.8 per cent for the second hour. At the time of onset of the toxic symptoms, 1.29 gm. of thiocyanate had been recovered in the urine, leaving a residual of 8.49 gm. A necropsy was performed. The anatomic findings were: lungs, congestion; heart, pericardial effusion, hypertrophy, inactive mitral stenosis and subendocardial hemorrhages; atheroma and ulceration in the abdominal aorta; kidneys, nephrosclerosis with profound arteriolar sclerosis, but no necrotizing lesions, and predominantly normal glomeruli; brain, edema.

The fresh tissues were analyzed for thiocyanate content. Table XII indicates the results of the analysis as compared with the tissue content in a patient who had not received the drug during life. These analyses were made by Dr. Kenneth Blanchard of the department of biology, New York University.

The second fatal case was that of a patient Mc., a woman, aged 56. Her hypertension was of the essential type. During the control period her blood pressure ranged from 220 systolic and 130 diastolic to 190 systolic and 100 diastolic. After receiving a total of 14.49 gm. in 18 days, an average daily dose of 0.805 gm., she complained of nausea. The thiocyanate was immediately discontinued. There had been no

^{*} Patient M. (see text).

appreciable fall in blood pressure. Forty-eight hours after the drug had been discontinued she developed nervous manifestations almost identical with those described in patient M. She persisted in this state for 6 days and died. Necropsy was not permitted.

In an attempt to explain the occurrence of toxic phenomena, one is first concerned with the dosage used. It might be expected that toxic manifestations would occur only when the larger dosages were given. That this is not so in the case of thiocyanate is clear from Table X. Severe toxic manifestations occurred in some patients who had received less of the drug, both in total and average daily dosage, than others who developed no toxic signs.

It further appears from our observations that in certain persons there is little or no margin of safety between the toxic and so-called therapeutically effective dose of thiocyanate.

We are of the opinion, therefore, that thiocyanate should not be administered to hypertensive patients for the purpose of lowering blood pressure, because, apart from its toxic effects, its influence is not striking in either the frequency or the extent of blood pressure reduction; that almost any medical or psychotherapeutic measure may be expected to yield results equally effective and with no element of danger.

What might be called the modern period of therapy began in 1923 with Daniélopolu. In 1875 Gull and Sutton published their report on arteriocapillary fibrosis. It was their opinion that widespread arteriolar sclerosis in the splanchnic area occurs first, and the obstruction to blood flow mechanically results in an increase in blood pressure.

Some years later Huchard⁵ and Allbutt⁶ took the opposing view. They noted, in independent investigation, that persons dying with hypertension might at necropsy show no significant arteriolar sclerosis. They concluded therefore that hypertension was the clinical expression of splanchnic functional vasoconstriction and that the arteriolar sclerosis was secondary to the elevated blood pressure.

Daniélopolu⁴ in common with most students of hypertension accepted this view. Since it was known that the sympathetic nerves carry vasoconstrictor fibers and since the splanchnic area is the largest vascular bed whose sympathetic nerve supply is accessible, he suggested and carried out the first sympathectomy for the treatment of essential hypertension.

In 1925 Adson7 stimulated interest in this operative procedure in

this country. At first the reports were highly enthusiastic. The first intimation that the results were not uniformly encouraging was the introduction of modifications of the operative procedure such as resection above the diaphragm, below the diaphragm, with and without partial resection of the adrenals and the celiac ganglion, and anterior nerve root section. Finally, Smithwick has introduced an extension of the technique for splanchnicectomy and sympathetic ganglionectomy.

As time went on, enthusiasm waned to the point now where applicants for this type of surgery are generally discouraged. As time goes on, more and more of those whose blood pressure had temporarily fallen have returned to their previous hypertensive levels. The one striking benefit has been the relief of incapacitating headache. Indeed, there are those who feel that even this and nothing more is full justification for the operative procedure in those in whom frequent paroxysms of headache have become intolerable.

Rytand⁸ studied forty patients before and after sympathetic surgery to evaluate if possible the subjective and objective benefits to be derived from this procedure. His conclusions reflect widespread present feeling, and are worth repeating:

"In general the results were poor. In only one patient was there a brilliant result, although in five others there was some degree of success in reducing blood pressure. Six more patients felt better, but their arterial pressures were not lowered. In nine patients there was no change. Eleven died within a year and a half, with their condition unchanged (transient relief of symptoms occurring in five of these). Eight died within two weeks of the operation. From a consideration of what is known about the pathologic physiology of arterial hypertension and the effects of denervation it would seem that not much could be expected from any such denervating operations."

In considering the rationale concerned with sympathetic surgery in hypertension you will remember that the first suggestion had to do with the observation that essential hypertension is a functional vasoconstrictive disease; that the vasoconstriction is principally confined to the splanchnic area; and that section of the splanchnic vasconstrictor nerve fibers might be expected to remove, if not the cause, certainly the anatomical pathway through which the cause becomes effective. It remained for Prinzmetal⁹ and Pickering, 10 working independently, to cast doubt upon the validity of some of these assumptions. Prinzmetal⁹

makes the following pertinent observations:

- "I. Determinations of resting blood flow in the arm in hypertension give an average value no greater than that obtained from subjects with normal blood pressure. This indicates that increased vascular resistance in hypertension is not confined to the splanchnic area but generalized throughout the systemic circulation.
- "2. Anesthetization with novocain of the vasomotor nerves to the arm produces the same increase in flow in normal subjects and patients with hypertension, proving that the vascular hypertonus is independent of the vasomotor nerves, and that this hypertonus must therefore be regarded as intrinsic spasm of the blood vessels themselves.
- "3. Surgical procedures aiming at the relief of high blood pressure by sympathectomy do not abolish the vascular hypertonus which is fundamentally responsible for the hypertension."

Increased blood pressure is one of the symptoms of hypertensive disease. It is influenced by many variables, some known and, very likely, some unknown. Since one of the known influences on blood pressure is sympathetic vasoconstriction, it is not surprising that widespread interruption of these impulses results in lowered blood pressure in some patients. It is reasonable to expect that the most marked postoperative falls in blood pressure will occur in those patients in whom extrinsic vasoconstriction contributes in greater part to the increased peripheral resistance. It is likely that the occasional so-called brilliant result is seen in patients in this category. Unfortunately, there is no unequivocal means of preoperative recognition of this more favorable group. In no sense, however, can sympathectomy be regarded as a cure of hypertensive disease. It does not remove the ultimate cause, but merely interrupts the pathway through which the cause is effective in producing one symptom of the disease, i.e., increased blood pressure, and even this effect, while undoubtedly beneficial, is not common and often temporary.

We now come to the present phase in the treatment of essential hypertension which is presumably based upon knowledge of the mechanism involved. This present phase of therapy was evolved entirely from observations on experimental hypertension in the animal. In 1933 Goldblatt and his associates demonstrated for the first time that persistent elevation of systolic and diastolic blood pressures could be induced in the animal by partial constriction of both main renal arteries.

Since this observation there have been many advocates of the thesis that human essential hypertension is on this same basis, namely, renal ischemia.

The observations which tend to support this simplified concept of hypertension in man would be acceptable in a given patient if:

- 1. Renal ischemia can be demonstrated to have preceded the hypertension.
- 2. Abolition of renal ischemia results in return of blood pressure to normal.

The first provision has not been established in man. The occasional observation in man of renal artery placques associated with hypertension is presumptive evidence only. As has been pointed out by Oppenheimer, Klemperer and Moschkowitz,11 it is just as reasonable to assume that the placque results from the hypertension as to assume that it leads to the hypertension. In the aged, where decrescent arteriosclerosis results in large wedgeshaped ischemic areas in the kidneys, diastolic hypertension does not occur. Furthermore, measurement of the rate of renal blood flow, the essential measurement in the critical examination of this question, is now possible. Not only are we in a position to measure the rate of renal blood flow, but also the amount of functioning renal tissue. A ratio of these two measurements would indicate the number of cubic centimeters of blood supplied to each unit of functioning renal tissues per minute. With this method, ischemia can be defined quantitatively and accurately measured. By means of this method the relationship between renal ischemia and hypertension can be more fully examined.

Drs. Chasis, Ranges, Bradley and I,¹² of the Department of Medicine, working with Dr. Homer W. Smith, Professor of Physiology at the New York University Medical College, have examined a group of patients with essential hypertension with these methods. We found that the hypertensive kidneys showed a diminished blood flow per unit of functioning renal tissue as compared with the normal kidney. However, it was concluded that the renal ischemia was a result of the hypertension and not its cause. This conclusion seemed amply substantiated by the observation that renal ischemia and hypertension could be produced in a normal subject by the administration of epinephrin or angiotonin; furthermore, in hypertensive subjects the renal ischemia is reversible under the influence of the pyrogenic reaction induced by foreign pro-

tein injection. One way to examine critically the relationship between the renal ischemia and elevated blood pressure would be to dispel the renal ischemia and note the effect on blood pressure. At the present this procedure cannot be applied to answer the question since the pyrogenic reaction employed to induce renal hyperemia so alters systemic hemodynamics as to make interpretation impossible.

Doctors Wellen, Welsh and Taylor¹⁸ of the Department of Obstetrics and Gynecology, using these methods, found that in toxemia of pregnancy at the height of the elevated blood pressure, the renal blood flow per unit of functioning renal tissue was normal, i. e., there was no ischemia. This observation is strikingly important to the question under discussion, since late pregnancy would seem to be the ideal situation for the development of hypertension on the basis of renal ischemia. Hypertension in specific toxemia occurs late in pregnancy when the uterus is large, and hydroureter and hydronephrosis due to pressure are common. Furthermore, in the great majority of such women there is a temporary or permanent fall of blood pressure to normal when the uterus is emptied. It would seem from these observations that in spite of the apparent reasonableness of the assumption, the hypertension of specific toxemia of pregnancy is not on the basis of renal ischemia. One might take the attitude that hypertension, like fever, is an expression of many causes and that renal ischemia might serve as the basis for the hypertension in a small number of patients. If this is true, therapy can be possible of success only if the hypertension in question is on a renal ischemic basis. Such therapy might be medical, as suggested by the present attempts with antipressor renal extracts, or surgical, by removal of a single diseased kidney, or a surgical procedure designed to increase the effective blood flow to the ischemic kidneys. Unfortunately, no distinction can be made now between human hypertension on a renal ischemic basis and hypertension on some other basis. There is one possible exception and that concerns the unilateral ischemic kidney. Drs. Chasis and Redish¹⁴ have made measurements of renal blood flow and renal mass for the detection of renal ischemia on each kidney separately, by means of ureteral catheterization. They have been good enough to allow me to use briefly one of their subjects. This Figure 1 shows ptosis and hydronephrosis of the right kidney. The patient has marked elevation of blood pressure. The only point I wish to make is that the renal blood flow and functioning renal mass are identical on both sides.

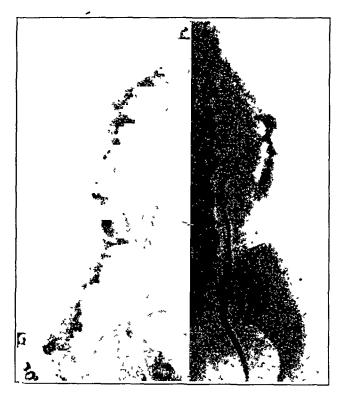


Fig 1—Retrograde pyelogram (erect position, anterior-posterior) showing angulation of right ureter with moderate hydronephrosis.

In other words, the apparently damaged kidney is not ischemic relative to the apparently normal kidney. Nephrectomy or any other surgical measure applied to the ptosed kidney for the treatment of the hypertension, would have been unwarranted.

The role of the kidney in the pathogenesis of hypertension and therefore the specificity of unilateral nephrectomy in its cure has been fully established for experimental renal ischemic hypertension in the animal. Whether or not this relationship obtains in man is still open to question.

A few highly enthusiastic reports suggest that occasionally a unilateral destructive renal lesion, such as congenital aplasia or atrophic pyelonephritis, may initiate the hypertensive process. Dr. Chasis and I have reviewed in detail every case report in the literature in which unilateral nephrectomy was performed for the cure of hypertension, or in which renal pathology in a hypertensive patient was indication for the nephrectomy; seventy-five such case reports have appeared in the litera-

ture to date. We regarded as acceptable demonstration of the beneficial effect of nephrectomy in hypertension, those patients in whom hypertension was established by adequate preoperative control and whose blood pressures fell to normal soon after nephrectomy and persisted in the normal range of at least one year. Of the seventy-five recorded cases, only eight fulfilled these criteria. Even this small apparently-successful group is not final proof that unilateral nephrectomy can cure hypertension, because high blood pressure may subside for long periods of time as a result of the non-specific effects of any surgical procedure.

The assumption in unilateral nephrectomy for the cure of hypertension, is that removal of an ischemic kidney eliminates the source of the pressor agent. When the blood pressure does not return to normal, it is assumed that the remaining kidney is ischemic, either as a result of unrecognized intrinsic disease or because of arteriolar sclerosis secondary to the preëxisting hypertension. I shall cite one patient in whom hypertension persisted in spite of complete abolition of renal ischemia. A 45-year-old white female was referred to Dr. Chasis by Dr. Edward Weiss, of Philadelphia. Measurements of blood flow and amount of functioning tissue were made on each kidney separately. In the right kidney the blood flow-tubular mass ratio (CD/TMD) was 8, indicating well marked ischemia, and in the left kidney there was practically no measurable blood flow or functioning renal tissue. The left kidney was removed and showed atrophic pyelonephritis. One month after nephrectomy Dr. Chasis repeated the measurements on the remaining right kidney and found a blood flow-tubular mass ratio of 12.2, which indicated a normal amount of blood reaching each unit of functioning tubular tissue, i.e., no ischemia. In spite of the complete elimination of renal ischemia the blood pressure level was unchanged and remained definitely elevated. The evidence presented throws considerable doubt on the concept of unilateral ischemic hypertension in man and consequently on the rationale of nephrectomy for its cure. Before closing this phase of the subject let me say that we believe it entirely logical that partial obstruction of one or both main renal arteries is capable of producing hypertension in man as in the experimental animal. This is well demonstrated by the published case of Leadbetter and Burkland. Their patient was cured during a 3-year follow-up period after removal of a kidney whose main renal artery was partly obstructed by a congenital muscle tumor. Their experience is unique and the only reported

instance of its kind. In our opinion it is not analogous to the far more common association of unilateral intrinsic renal disease and hypertension in which we believe the renal disease and hypertension are not related.

In accordance with the assumption that hypertension in man is initiated by renal ischemia, two other operative procedures have been suggested and tried. Renal-omentopexy to supply a new source of blood to the kidneys and nephropexy to correct interference with renal blood flow presumably due to ptosis of the kidney with kinking of the ureter.

Unilateral renal-omentopexy was performed on two patients at Bellevue Hospital, by Dr. Arthur Wright. The functional measurements, made up to 18 months after operation, indicated that blood flow to the operated kidney was actually decreased by a surgical procedure designed to do the opposite.

In another patient with marked nephroptosis, nephropexy was performed by Dr. Howard Jeck. Again the measurements made 12 months postoperatively showed a diminution of blood flow in the operated kidney. In neither of these patients was the blood pressure lowered.

At the present time considerable interest is centered on two nonsurgical measures designed to reduce high blood pressure, both presumably directed toward the initiating mechanism. One is concerned with the antipressor effect of renal extract and the other with completing the process of deamination.

Treatment with a renal extract has its basis in a number of experimental observations which suggest that normal renal tissue contains a substance capable of opposing the pressor action of angiotonin or similar pressor substance liberated from an ischemic kidney. It presupposes therefore that essential hypertension in man is initiated by a pressor mechanism originating in a manner analogous to that which obtains in the renal ischemic animal. This material is being administered to patients parenterally by Page and his associates and orally by Grollman and his associates. Both groups have been cautious in their interpretation of the results in man. Page and his associates indicate only that "the extracts may have merit." Extensive clinical trial has been handicapped by the difficulties inherent in the manufacture of an adequate amount of active material. Furthermore, alarming instances of peripheral circulatory collapse have occurred following parenteral administration. Before final estimate is possible, an extract free of impurities will have to be

administered to a larger number of hypertensive subjects. In the light of our own present opinion that there has been no demonstrated analogy between human and experimental hypertension, data on treatment with the extract cannot logically be transferred from animal to man. A further barrier to the acceptance of the specificity of renal extracts is the well-known fact that blood pressure can be lowered by the parenteral administration of any foreign protein. Drs. Chasis and Smith and I17 have demonstrated this with the administration of typhoid vaccine, intravenously and subcutaneously. The pyrogenic reaction which occurred with each adequate dose was followed by marked temporary fall in blood pressure and on two occasions with falls to shock-like levels, as described with renal extracts by Page and his associates.15 By daily administration of typhoid vaccine it was possible to maintain a distinctly lowered blood pressure indefinitely. Although premedication with amidopyrine prevented the chill and fever components of the pyrogenic reaction, it was just as effective in lowering the blood pressure. We concluded that this hypotensive effect was due to widespread acute vasodilatation and represented an unphysiological and therefore undesirable effect. It must be emphasized, however, that although renal extracts may owe part of their effect to a non-specific pyrogenic reaction, a specific antipressor action may still be operating.

The second non-surgical and presumably specific therapy is based upon the thesis that ischemic renal tissue is deprived of adequate oxygen. As a consequence amines would not be deaminized, and since they are known to be pressor, their accumulation in the blood would result in hypertension. To correct this metabolic fault it has been suggésted that amine oxidase be administered. The observations of Holtz¹⁸ and Bing¹⁹ have established the probable validity of this hypothesis. Schroeder²⁰ has made observations on man with tyrosinase and Soloway, Oster, Friedman, Marrus and Oppenheimer^{21,22} in rats, using certain quinones. The effect on the experimental hypertension of rats, while striking, is subject to the same difficulty of interpretation as with renal extract in the hypertensive dog, i.e., that the mechanisms of human and experimental hypertension have not been shown to be analogous. In attempts to reduce the blood pressure in hypertensive humans with Tyrosinase we encountered the pyrogenic reaction which obscured any specific antipressor effect which may have been concomitantly present. For a final estimate of its value in human hypertension, as with renal extracts,

further trial is necessary with an amine oxidase free of pyrogenic agents, and the observations must be made in man.

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PULMONARY IRRITANTS*

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CLASSIFICATION OF PULMONARY IRRITANTS

group of compounds that exist as gases, or as liquids that have a sufficiently high vapor pressure under ordinary conditions to give rise to injurious concentrations in respected air.

Of greatest interest among these, for the purposes of the present discussion, are the acid gases-substances that appear to owe their physiological effects to the fact that they are acids or that they behave like acids under the conditions of their use-these being hydrogen chloride, bromide and fluoride, and chlorine, bromine, sulfur dioxide and certain oxides of nitrogen, together with phosgene, diphosgene and chloropicrin. There are other less common members of this group, and there are also non-irritant, unstable alkyl halogen compounds that exert their primary effect upon the nervous system when inhaled, subsequently, and apparently through hydrolysis, yielding substances that act as irritants, inducing extensive circulatory and pulmonary damage. Whether the pulmonary damage in the latter group is due mainly to circulatory failure, or to the exhalation of an irritant decomposition product of the original compound has not been established, but the lung pathology is so like that caused by the inhalation of an irritant gas as to justify the inclusion of these compounds in this group.

Next, come members of the group classified for the purposes of chemical warfare as vesicants. The best known among these, mustard and lewisite, must be regarded as pulmonary irritants in the toxicological sense, since despite their low vapor pressure, they give rise at ordinary temperatures to highly irritant concentrations of vapor. The serious pulmonary injury sustained by persons who inhale these vapors does

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not lend itself to satisfactory explanation, and nothing will be said concerning its pathological physiology in this discussion. The injurious effects of the inhalation of these vapors must be mentioned, however, because of the pattern of the clinical condition that develops—a pattern that is different in many respects from that associated with exposure to the acid gases. These effects will be dealt with briefly at an appropriate time.

Certain other gases, of which ammonia and formaldehyde may be mentioned as examples, do not fit into either of the preceding groups. Inhalation of these substances in sufficiently high concentrations induces the symptoms and the pathologic picture of acute upper respiratory and pulmonary irritation. They are mentioned only to call attention to the fact that this classification of irritant respirable substances is of necessity somewhat incomplete.

Finally, the carbonyls would seem to come within a toxicologic classification of pulmonary irritants, because of their property of depositing finely divided particles of metal in the lung tissue, thereby inducing an intense pulmonary irritation and edema. Iron and nickel carbonyl represent the best known examples of this group. For a variety of reasons these compounds scarcely seem destined to play an important role in chemical warfare, and therefore they are mentioned only as interesting examples of an additional and apparently unique type of pulmonary irritant.

CERTAIN PROPERTIES OF PULMONARY IRRITANTS

Correlation and comparison of certain of the physical, chemical, and physiological properties of some of the substances referred to in the foregoing paragraphs will serve to illustrate practical points of importance.

Table I calls attention to the importance of volatility in determining the comparative potentialities of compounds that have about the same toxicity (compare mustard and the potentially more dangerous lewisite), while at the same time it shows how unimportant relative volatility may be when a compound is sufficiently toxic (compare chlorine with mustard).

Table II demonstrates how little relationship there may be between the actual toxicity of one of these compounds, and the immediately painful sensation of upper respiratory and pulmonary irritation that

TABLE I

COMPARISON OF VOLATILITY AND LETHAL

CONCENTRATION OF IRRITANT AGENTS

| | Concentration in milligrams per liter | | | | | | |
|-------------------------------|---------------------------------------|--------------|----------|---------|----------|--|--|
| | Phosgene | Chloropicrin | Chlorine | Mustard | Lewisite | | |
| Vapor in air at 20° C | ∝ (gas) | ∝ (gas) | ∝ (gas) | 0.57 | 4.50 | | |
| Fatal for 30 min. of exposure | 0.36 | 0.80 | 2.50 | 0.07 | 0.05 | | |
| Fatal for 10 min. of exposure | 0.50 | 2.00 | 5.60 | 0.15 | 0.12 | | |

TABLE II

COMPARISON OF MINIMUM DETECTABLE, IRRITATING AND LETHAL CONCENTRATIONS OF IRRITANT AGENTS

| | Concentration in milligrams per liter | | | | | |
|----------------------------------|---------------------------------------|--------------|---------------|---------|----------|--|
| , | Phosgene | Chloropicrin | Chlorine | Mustard | Lewisite | |
| Minimum detectable odor | 0.0044 | 0.007 | 0.01 | 0.0013 | 0.014 | |
| Minimum irritating concentration | 0.005 | 0.009 | 0.029 | 0.001* | 0.008* | |
| Fatal for 10 min. of exposure | 0.50 | 2.00 | 5. 60′ | 0.15 | 0.12 | |

^{*} There is a latent period before presence is apparent.

result from exposure to it. In practical terms this means that not all of them give adequate warning of their presence in dangerous concentrations in the respired air.

Still other properties of these substances are important factors in their behavior. Their solubility in water, or the avidity of their combination with water, may be the determining factor in the locus of their action. Thus the primary effect of exposure to the highly soluble chlorine, ammonia, and sulfur dioxide is exerted upon the upper respiratory tract, and if one is exposed to low or moderate concentrations for periods that are not too long, the damage done is confined almost entirely to the nose and throat. In contrast, the chief injury associated with the inhalation of correspondingly irritating concentrations of phosgene occurs in the lung.

THE GENERAL EFFECTS OF EXPOSURE TO PULMONARY IRRITANT GASES

Much has been made of the importance of the time-concentration relationship in exposure to noxious gases, and in general emphasis upon this relationship is justified. A certain caution must be exercised against complete reliance upon it. The duration of the exposure to an highly irritant gas is important, but the severity of the effect cannot be expressed as the product of concentration and time, except within certain limits of concentration, because of the disproportionately injurious effects of brief exposures to high concentrations, as well as the negligible effects of sufficiently low concentrations. This can best be appreciated if it is recognized that there are at least four, and perhaps five, types of effect that result from various combinations of concentration and length of the exposure.

- 1. The effect of exposure to very high concentrations may be virtually immediate anoxic death. Whether this outcome is the result of direct damage to the respiratory membrane rendering it impermeable to the normal respiratory gases, whether it is due to rapid absorption of the poison with central respiratory paralysis, or whether it is due to circulatory collapse (vagus shock), is not apparent. The pathological picture in experimental animals suggests that the last mentioned possibility is the most likely.
- 2. Another result of brief exposure to high concentrations of these gases, which may differ only in degree from that previously described, is extensive immediate damage to the pulmonary and upper respiratory tissues. Acute hyperemia, hemorrhage and tissue destruction (coagulation necrosis) may be the prominent features of the pathological picture, or alternatively, if death occurs promptly, there may be acute emphysema, general acute interstitial edema, ischemia and coagulation necrosis. In this and in the previously mentioned type direct pulmonary injury is much more prominent than reaction to injury or the secondary effects, chiefly because death occurs before these have time to develop.
- 3. The third group of effects is that with which we are most concerned in that it offers an opportunity for survival. Here, there is pulmonary injury of a serious type, and accompanied by upper respiratory damage that varies in degree with the nature of the agent and its concentration in the air breathed by the victim. It is to this general set of effects that we shall give detailed consideration.

- 4. A fourth type of effect is that following exposure to concentrations of noxious substances that are insufficient to cause immediately serious injury to the respiratory tissues, over such a period of time as to cause accumulation of these noxious substances in the tissues of the body as a whole and thereby to induce systemic intoxication. This type of effect is of no practical importance in relation to chemical warfare. It is of some interest, however, to recognize that a dangerous and even lethal dose of an acid gas may be absorbed from the respired air without doing greater damage to the lungs than to the other organs.
- 5. A still further set of effects is that produced by mild exposures to respiratory irritants for comparatively short periods, following which the injury is limited almost entirely to irritation of the eyes and upper respiratory tract. There is stinging and burning of the eyes, nose, and throat, redness and weeping of the eyes and the respiratory and pharyngeal mucosa, sneezing perhaps and certainly coughing, with a sore throat and huskiness or perhaps loss, of the voice. There may be headache, originating from irritated accessory nasal sinuses. Nosebleed is not infrequent, and there may be some blood-tinged sputum from the pharynx and trachea, but there will be little chest pain except perhaps the muscular soreness associated with excessive coughing. These effects last from a few minutes to several hours, with more prolonged lesser effects, among which the soreness of the throat and the huskiness of the voice may be the most persistent.

THE EFFECTS UPON THE RESPIRATORY SYSTEM OF SERIOUS EXPOSURE TO IRRITANT AGENTS

Immediate effects: The initial symptoms of exposure to irritant gases are those of sharp burning pain in the eyes, nose and throat, with constriction of the throat, irregular respiration, followed by rapid, dyspneic respiration, and subsequently by some degree of relief as the secretions of the eyes and nose begin to flow and bathe the irritated surface. The severity of these symptoms varies with the characteristics of the agent involved, and with the concentration to which one is exposed. Labored breathing with spasmodic coughing may be prominent, and chest constriction and pain, with air hunger and the fear of promptly impending death, may develop. Upon escape from exposures of less than extreme severity, there is some degree of relief from the more acute distress, but the coughing continues for some time, producing considerable mucus

which is likely to be blood-tinged and may be frankly hemorrhagic, and the burning of the nose and throat continues. The voice becomes husky and may be reduced to the merest whisper. Gradually some degree of comfort ensues in most cases.

Effects during following twenty-four hours: After two to twelve hours of relative comfort, respiratory distress, accompanied by the increasing physical signs of pulmonary moisture, may begin to develop, and may reach an acute stage promptly, especially if the victim exerts himself in any way. There may be no interval of relief; in such cases the signs of acute respiratory irritation during exposure are followed by steadily increasing signs of pulmonary congestion and edema or hemorrhage. On the other hand, there may be a gradual subsidence of all of the symptoms of upper respiratory and pulmonary irritation, with little or no evidence of pulmonary edema. Exposed persons, kept under observation over a period of twenty-four hours during which pulmonary congestion and edema have failed to appear, may generally be regarded as free of danger. This period of twenty-four hours following the exposure is crucial, and for such a time the patient must be kept quiet and warm, as comfortable and relaxed as possible, and under careful observation. It is probable also that this is the period during which specific measures for the prevention of pulmonary edema will be indicated, if and when such measures can be developed on a sound physiologic rationale.

Subsequent effects: Exposed persons who do not develop evidences of pulmonary edema within the first twenty-four hours will recover promptly and without further incident, as a rule.

Those who develop pulmonary edema may be ill for periods that vary from a few days to many weeks, dependent upon the severity of the injury sustained. Secondary infection resulting from the invasion of the bacterial flora of the nose and throat into the injured tissues may be expected to develop in the individual who survives the acute chemical injury, and infectious tracheitis, bronchitis, bronchopulmonary abscess, and bronchopneumonia are very likely to follow. Death may occur at any of these stages in the process.

PULMONARY EDEMA

Since the occurrence of pulmonary edema is the outstanding clinical sign that serious damage to the lungs has occurred as the result of ex-

posure, and since the course and the degree of severity of the pulmonary edema are the most decisive factors in the survival or death of the injured person, we are justified in concentrating our chief attention upon its genesis and development.

Onset: As indicated previously, the onset of pulmonary edema following exposure to irritant gases, may be prompt or it may be delayed for as long as twelve hours. In the young and healthy individual, the longer its appearance is delayed the less likely it is to develop. The outlook is uncertain to some degree in the old or in persons who are the victims of chronic respiratory and circulatory diseases, and therefore the effects of exposure on the part of the civilian population cannot be anticipated with complete assurance on the basis of the experience of armed forces in the last war. The latent period between the occurrence of the exposure to irritant gases and the onset of the edema can best be understood by visualizing the effects induced by contact of the irritant agent with the respiratory tissues.

Pathology: The general character of the injurious effect of the pulmonary irritants (omitting any present references to the effects of exposure to mustard and lewisite) as well as the reaction on the part of the tissues to such effects, is the same throughout the respiratory system. The results differ widely, however, because of the differences in the structure and vascularity of the various parts of the system. Cellular edema, coagulation necrosis and disintegration, hyperemia, congestion, transudation, exudation, diapedesis, hemorrhage, focal necrosis, thrombosis and infarction occur in varying proportions at different sites and times, to make up the whole pathological picture.

In the upper respiratory tract there is a general inflammatory reaction with first a serous, and later perhaps, a sero-sanguineous discharge, and still later ulceration, hemorrhage, exudate and fibrin. Plugs of debris may obstruct larger and also smaller air passages. Later, after the development of pulmonary edema, the trachea will be filled with frothy, watery, perhaps sanguineous fluid, and when pneumonia develops, with a purulent or fibrino-purulent exudate.

In the lung similar damage occurs to the bronchioles and alveolae, on a smaller scale. The picture seen at necropsy depends to a very large degree on the time at which death occurs. The damage is likely to be spotty, rather than general, certain areas being preserved from direct injury by reason of bronchiolar spasm, others being atelectatic or eminipury

physematous, because of complete or partial obstruction with debris. At first, emphysema, petechial hemorrhage, perhaps confluent hemorrhage, and interstitial edema predominate. Later, large and small areas of deeply congested lung tissue may be seen to be heavy, boggy, and dripping with a thin sanguineous fluid. These may become virtually confluent, the entire lung being large and very heavy, with water running from the cut dark red surface, and with frothy islands of fluid appearing from the cut bronchioles when slight pressure is applied. If death has occurred some days after the onset of the edema, there will be areas of pneumonic consolidation. These may be in any stage of development or resolution dependent upon the time interval between the exposure and death. There may be abscesses or gangrene. Still later, pulmonary fibrosis as well as chronic bronchitis and bronchiectasis may be seen.

The pathological findings are by no means limited to the respiratory system. A later discussion of the pathological physiology of pulmonary edema will show that when death occurs during that stage, it is the result of anoxia and circulatory failure. Accordingly the general signs of circulatory collapse, with widely dilated heart (especially the right side), passive congestion, and venous stasis are very prominent. In addition, the lesions of an acute toxic process—edema, hyperemia, petechial hemorrhage, and focal necrosis—will be found to greater or lesser degree in other organs, notably the kidneys, liver, heart muscle and brain. The systemic effects of the absorption of phosgene, for example, may not be ignored, and would not be reduced to secondary importance except for the overwhelmingly dramatic character of the pulmonary pathology. The blood is dark in color, reduced in volume, and very viscid through hemoconcentration. Capillary thromboses may be seen, and thrombi may be found in larger vessels.

Pathological Physiology: The genesis and the development of the pulmonary and systemic picture may be considered sequentially, in terms of the chief effect—that of the production of anoxia. If it be recognized that bodily requirements in way of oxygen may be met in a variety of normal and unusual circumstances through the joint response of the respiratory and circulatory apparatus, the difficulty presented by gross impairment of the respiratory system will become more apparent. The normal respiratory system can increase its capacity for ventilating the blood some twelvefold or more, while the minute-volume of the circulatory flow can rarely be increased to more than ten times its normal

resting level. The type of injury to the respiratory system with which we are concerned here may deprive the organism of any respiratory reserve soon after exposure, and may well progress to a point where respiration is too ineffectual to sustain life. The large air-ways may be partially obstructed, first by muscle spasm and later by debris, fluid, and froth; large numbers of bronchioles and alveolae may be closed off or filled up with debris, exudate, hemorrhage and fluid; the lung volume is further reduced by atelectasis, consolidation, and fluid; the effective respiratory volume is reduced by maintained, shallow respiration on an expanded, emphysematous chest; the diffusion of oxygen through a greatly reduced area of respiratory membrane is still further hindered by an edematous thickening of that membrane; and the utilization of the limited oxygen supply in the blood is lowered by reason of the reduced oxyhemoglobin dissociation occasioned by the low carbon dioxide tension of the peripheral blood. (The decreased carbon dioxide tension is produced by the relative ease of diffusion of carbon dioxide, aided by the overventilation of intact and unobstructed alveolae.) Every mechanism whereby the available oxygen of the blood can normally be increased is impaired, and the result may well be that the maximum respiratory exchange, in so far as this is mediated by the respiratory apparatus alone, may be greatly reduced below the normal resting capacity. The result obviously is anoxia-an anoxia which can be offset by physiological mechanisms and at normal atmospheric conditions only through increased circulatory activity.

It may be worth while at this point to call attention to the fact that pulmonary edema as we are dealing with it here is the exact antithesis of that more commonly seen in the terminal stages of circulatory failure. The latter arises primarily out of circulatory failure and is a sign of impending death; the former is due to direct chemical injury to the lung, the general circulatory system exclusive of the intrinsic pulmonary circulation being essentially intact. The maintenance of an efficient circulation is seen therefore, to be of paramount importance. Unfortunately the intrapulmonary vascular bed will have suffered damage comparable to that sustained by the pulmonary epithelium, and thereby the circulatory system will have been embarrassed at the point at which the gaseous exchange occurs. With the onset of pulmonary edema there comes further embarrassment in that the water and serum loss into the lung tissue concentrates the blood, decreasing its volume and increasing its

viscosity, thereby promoting stasis and capillary thrombosis. All of these factors, in addition to the reduced interchange of respiratory gases incident to the direct pulmonary damage, throw an increased burden upon the heart.

The sequence of the circulatory changes that may be expected to occur merits special attention. The initial response to anoxia is seen in an increase in cardiac rate and output, the heart remaining approximately normal in size, the arterial pressure increasing in both systemic and pulmonary systems, and the venous pressure showing a moderate increase. So long as the tissue anoxia is readily compensated in this manner, no further qualitative change occurs, but as the edema incident to the pulmonary injury increases, anoxia progresses and the cardiac burden increases. The resistance in the pulmonary circuit increases also, and the load on the right heart becomes disproportionately great. As a consequence of this situation, the right heart increases in volume while the left decreases, the systemic arterial pressure-especially the diastoliccontinues to increase, the pressure in the pulmonary artery is still further increased, the venous pressure mounts to high and yet higher levels, the pulse rate increases, and the minute-volume cardiac output decreases to something less than its maximum. At this time there will be capillary dilatation due to the high capillary and venous pressure, and perhaps to some elevation of the carbon dioxide tension, the skin being warm and florid or purplish (cyanosis) in color.

If now the pulmonary edema does not progress, the circulatory system may be capable of maintaining its load successfully, and with the onset of the healing process, survival and recovery may result. If the injury has been sufficiently severe, however, or if the heart begins to fail, the picture changes gradually or perhaps suddenly. The most striking features of the change are dilatation of the right heart, a drop in the venous pressure, a drop in the systemic arterial pressure, the development of a rapid, thready pulse, and the appearance of a grayish, perhaps slightly bluish pallor, with coldness and clamminess of the skin, especially of the extremities.

Clinical Types: An adequate discussion of the variations in the clinical picture that result from exposure to different agents would require much more precise information than is available from industrial experience, from the clinical observations of the First World War, and from animal experimentation. Some few comments may be warranted for

their practical usefulness. Comparison of chlorine, phosgene, and chloropicrin, mustard and lewisite reveal a number of distinct differences.

Exposure to effective concentrations of chlorine results in acute painful injury to the upper respiratory tract, together with somewhat less serious damage to the lungs. Pulmonary edema develops with little or no delay, and reaches its climax within twelve to twenty-four hours. Delayed deaths may result from secondary infection, but apparently not because of general or localized toxic effects in the viscera.

Exposure to phosgene causes little upper respiratory injury or discomfort, and there is a latent period of apparent comfort before pulmonary edema develops. The edema develops rapidly, however, after the onset, most of the deaths occurring within the first twenty-four to forty-eight hours. Delayed deaths occur as the result of pneumonia and also because of toxic damage to the heart muscle and the brain as well as to the liver and kidneys.

Exposure to chloropicrin causes less injury to the upper respiratory tract than chlorine, and more than phosgene. The damage induced by it in the medium-sized to small bronchi is great, with the result that an acute bronchitis develops early. Pulmonary edema also develops promptly, the effect of this agent resembling chlorine in that respect.

Exposure to mustard gas by inhalation of vapors produces acute injury and inflammation of the entire respiratory tract, followed by necrosis and desquamation of the mucous membrane and pulmonary epithelium. A diphtheritic membrane forms on a mucous surface, and a lobular pneumonitis develops, with plugging of bronchioles followed by the formation of bronchopulmonary abscesses that quickly come to the surface, inducing pleuritis and locular empyema. The generalized pulmonary edema associated with exposure to the agents classified as pulmonary irritants, is not a conspicuous part of the picture.

Clinical information on the effects of the inhalation of lewisite by human beings is not available. From observations on dogs it would seem that the type of injury and inflammation resembles that produced by mustard gas, with the exception that there is somewhat greater pulmonary edema. Secondary infection, bronchopulmonary abscess and bronchopneumonia develop promptly and are the most striking features of the pulmonary pathology. Petechial hemorrhages, and other toxic changes in the liver and kidneys give evidence of the general intoxication that might be expected to result from the absorption of this organic arsenical compound.

TABLE III

THE CLINICAL CHARACTERISTICS OF THE BLUE AND GRAY TYPES OF CYANOSIS

| Symptom or Sign | Blue or Florid Cyanosis | Gray or Pallid Cyanosis |
|-------------------------|---------------------------|-------------------------|
| Respiratory rate | 40—50 | 50 |
| Pulmonary moisture | Present | Present |
| Arterial blood pressure | Normal or elevated | Low |
| Venous pressure | High | Low |
| Pulse | 100—full | 130—thready |
| Temperature | 100—101 | May be subnormal |
| Temperature of skin | Warm | Cold—clammy |
| Headache | Present | Present |
| Mental state | Restless and apprehensive | Restless and delirious |

The clinical types of pulmonary edema that are more commonly referred to, in connection with the effects of exposure to the pulmonary irritants, are differentiated on the basis of the onset and the development of the picture without regard to the specific agent responsible for the injury, as (1) latent, (2) blue cyanotic and (3) gray cyanotic types. There is the more reason for employing this classification rather than that based on the specific agents, since the latter may well be used in mixtures.

- 1. The latent type has been referred to previously, especially in connection with the effects of phosgene. Despite the fact that the serious symptoms of pulmonary edema tend to develop soon after exposure in most instances, it is necessary to be on the lookout for exposed persons who appear to be practically free of symptoms only to develop labored respiration and circulatory embarrassment within a few hours. This condition may be revealed dramatically by the collapse of an individual who, having attempted some task involving moderate or even slight exertion, has exceeded his scanty respiratory reserve.
- 2. The type of case classified as having a "blue" cyanosis, is one in which the individual has an anoxemia sufficient to give rise to cyanosis, and obviously, therefore, is suffering from some degree of tissue anoxia. The degree of the anoxemia, and of the general anoxia, is difficult to estimate from the appearance of the patient, since the thickness and

color of the skin, the richness of the circulatory supply, the intensity and quality of illumination, and many other factors, influence one's observation. About 5 grams of reduced hemoglobin are required to produce cyanosis, and therefore, obvious cyanosis must be regarded as evidence of a significant degree of anoxia. The significance of the blue cyanosis, otherwise spoken of as purplish or florid cyanosis, has been pointed out in the discussion of the pathological physiology. The chief clinical characteristics of this state are summarized in Table III.

3. The "gray" cyanotic type is characterized less by the cyanosis, which may be difficult to see, than by the obvious ashen pallor which is associated with circulatory failure. It is thus referred to as the pallid type of pulmonary edema. The associated clinical phenomena of this condition, as given in Table III, show its grave character. When it appears early in the course of the illness, it denotes either extensive pulmonary damage, or the existence of a crippled circulatory system; when seen as a late manifestation, it is only slightly less ominous, since it shows cardiac weakness.

THE SEQUELAE OF INJURY INDUCED BY PULMONARY IRRITANTS

The sequence of events following exposure to irritant agents has been indicated in sufficient detail to delineate the course of the clinical condition. Death may occur at any of the stages indicated, or the edema may clear up, the pneumonia may be resolved, and complete recovery, without residual effects of any kind may take place. The length of time required for this result depends upon the degree of pulmonary injury sustained and upon the nature of the complications that develop. In addition to the secondary infection which in some degree is almost inevaluable, other factors such as age, chronic respiratory disease (bronchial asthma, chronic bronchitis, tuberculosis), diseases of the circulatory system, and trauma, must be considered in the case of civilian casualties.

The sequelae, likewise, will be influenced in frequency and severity by all of the factors mentioned above. The experience of the First World War has shown that complete recovery was the rule among young, healthy persons who survived the acute effects of exposure to pulmonary irritant gases. For a number of reasons the incidence of permanent disability may be expected to be higher among the unselected victims of gas attacks carried out against the general population, but such disability should be relatively infrequent if casualties can be given adequate

care at the proper time. Certain neuroses will be seen, if past experience can be relied upon, and the frequency of these will depend in large measure upon the extent to which the public is taught, led and advised in such matters. In other words, panic and unrestrained fear of mysterious and horrible effects that are thought to result from exposure to war gases, provides a fertile soil for the development of neurotic manifestations.

The sequelae that have been described among soldiers are pulmonary fibrosis, chronic emphysema, chronic bronchitis and bronchiectasis, all of which are the result of infection rather than chemical injury, together with two other disturbances, which in at least some instances are partially functional and which cannot always be clearly distinguished from each other. One of these, generally known as "effort syndrome," is very like "soldier's heart" and is so spoken of by some writers; the other is characterized by recurrent attacks of nocturnal dyspnea. In effort syndrome, as indicated in the expression, the patient becomes exhausted by an insignificant expenditure of effort. Headache, vertigo, precordial pain, dyspnea and tachycardia are the outstanding complaints. The attacks of nocturnal dyspnea are associated with little or no evidence of organic disease of the chest. There is usually an increase in the number of erythrocytes and in the hemoglobin content of the blood. This phenomenon suggests that there is chronic anoxia, due perhaps to rapid shallow breathing, but it is said that no cyanosis is present. Further study of cases of this type would seem to be required to elucidate their physiological background.

THE TREATMENT OF PULMONARY IRRITATION AND EDEMA

First aid treatment of casualties consists of maintenance of quiet and warmth until transportation in the recumbent position can be accomplished. In view of the nature of the condition, persons regarded as casualties should not be permitted to walk or even to sit up, but should be moved on a stretcher as soon as possible to the point at which medical examination and treatment can be instituted. They should be covered up with blankets to prevent chilling, and in addition warm drinks may be administered if desired. Artificial respiration must not be given even to persons in acute respiratory distress, and decontamination should be limited to simple, quickly completed measures such as, clipping off the hair, cutting away clothing, and removal of any agent that may involve

obvious hazard to life or vision.

No treatment for the prevention or relief of pulmonary edema is available at present. Relief of the anoxia may be accomplished satisfactorily in many instances by the administration of oxygen. So long as cyanosis can be prevented by this means, this form of treatment is satisfactory, in that it combats the anoxia, prolongs life, and perhaps tides the patient over a critical period. The administration of oxygen may be carried out in various ways dependent upon the facilities available for the purpose. The use of a nasal catheter is perhaps the best when special equipment is not available. By this means the oxygen tension of the inspired air can be trebled. In well developed pulmonary edema, it may be necessary to resort to the administration of oxygen in a closed inhalation system under pressure. Self-contained portable and fixed inhalation equipment, and various types of masks are available for use with oxygen or with oxygen-carbon dioxide mixtures. The best results can be obtained only by carefully trained personnel. Indeed the success of any efforts made to employ oxygen therapy in this condition will depend upon the training and experience of attendants.

There is considerable disagreement as to the usefulness of venesection in the treatment of pulmonary edema. One may be dubious of the rationale of reducing the volume of the circulating tissue under conditions in which it is destined to be reduced by transudation from a large injured capillary bed. On the other hand, one may be justified in believing that the relief of the high venous pressure associated with the stage of florid or blue cyanosis is a valuable albeit a temporary measure. That any benefit can accrue from attempts at blood-letting in the stage

of gray cyanosis, seems impossible.

Prevention and treatment of the infection that may follow this type of upper respiratory and pulmonary injury, will be indicated in accordance with the best methods available. The use of sulfonamide drugs may offer means, not formerly available, to cope with this formidable complication. Perhaps caution against an excess of optimism may be justified here, however, since the organisms involved in such infections will be those harbored in the nasopharynx of the victim, rather than those that would be expected in more common types of nasopharyngeal and pulmonary infections. Arsenicals may be indicated in pulmonary abscess with gangrene associated with spirochetal infections.

Other forms of treatment will be wholly non-specific and presum-

ably symptomatic. General supportive treatment, and careful avoidance of exertion are necessary. Apprehension should be relieved by persuasion as far as possible, but when anxiety and restlessness reach a stage where more vigorous control is required, the disadvantages associated with the use of sedatives, including morphine, will be counterbalanced by their beneficial effect. Heart stimulants may be required and should be used as indicated, caffeine being especially recommended.

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THE EFFECT OF WAR GASES AND OTHER CHEMICALS ON THE EYES OF THE CIVILIAN POPULATION*

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B gases may injure the eyes of the civilian population these as well as war gases will be considered in this paper. However special emphasis will be placed on the diagnosis and treatment of eye injuries by war gases.

WAR GASES

The first record of the use of noxious gases is by the Spartans against the Athenians in 431-404 B. C.¹ Gas was first used by the Germans in April, 1915, in a surprise attack against the Allies in Flanders. The casualties were high because the troops had no protection. Since gas was found to be an efficacious military weapon its use became widespread during World War I but fortunately efficient protection was rapidly developed. More recently gas was reportedly used by the Japanese against the Chinese and by the Italians in Ethiopia when mustard gas oil was sprayed from airplanes. It is possible that the horrors of gas warfare will be brought to the general population at some time in the future even though there is a question of how efficacious such use of gas may be in winning a war.

Although we have little information concerning the effect of war gases on the civilian population, we do know much concerning the effect of these gases on the eyes (1) from experience in the last war, (2) from accidents in factories manufacturing war gases and (3) from experiments with animals. These three sources of information have been

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TABLE I

CHART SHOWING NUMBER AND PERCENTAGES OF CASES OF
BLINDNESS IN WORLD WAR I FROM GAS AND NON-GAS
WEAPONS (GILCHRIST2)

| Nature of Injury | Cause | Number | Per Cent |
|---------------------------|----------------|--------|-----------|
| Loss of right eye | Gas | 16 | 1.9 |
| | Non-gas | 307 | 37.8 |
| Loss of left eye | Gas | 10 | 1.2 |
| | Non-gas | 289 | 35.6 |
| Loss of both eyes | Gas Non-gas | 4 41 | .5 5.3 |
| Loss of one eye (unknown) | Gas | 3 | .4 |
| | Non-gas | 59 | 7.3 |
| Traumatism | Gas | 0 | .0 |
| | Non-gas | 80 | 0.01 |
| Total | Gas | 33 | 4.0 |
| | Non-gas | 779 | 96.0 |

used in preparing this outline of injuries of the eyes which might be expected if gas warfare is brought to the civilian population.

On the whole, war gases have not proved to be very harmful to vision in a permanent way. In World War I of 812 blind or partially blind soldiers, 4 per cent of the injuries were the result of gas weapons while 96 per cent resulted from non-gas weapons. Gilchrist² has tabulated these cases in Table I.

Derby's³ experience in World War I showed that from 75 to 80 per cent of the eyes affected by gas were only mild cases. Parlange⁴ reported the following incidence of eye affections: three corneal ulcerations in 1500 gassed individuals; two corneal opacities in 1800 gassed individuals and 700 conjunctivitides in 4000 gassed individuals.

For practical purposes all known gases may be divided according to their actions into five groups: (1) vesicant, (2) lung irritating, (3) sternutatory, (4) lacrimatory and (5) toxic gases.

Many known war gases are capable of causing irritation, and direct or indirect injury to the eyes but practically mustard gas and lewisite are the only important ones from the standpoint of direct eye injuries. Individuals with previous eye lesions, e. g., trachoma, keratitis or old corneal scars, suffer more acutely from contact with gas than do persons with normal eyes.⁴ It is sometimes difficult to be sure to which gas a person has been exposed and shells combining mustard, phosgene and tear gas were used in World War I.⁵ Another method of using gas at the time of the last war was to release shells containing sternutatory gases which would force the soldiers to remove their masks and then to release lung irritating gases. At that time the respirators afforded no protection against sternutatory gases, but present masks do since a paper filter was inserted.

VESICANT GASES

Mustard Gas: In the first World War mustard gas was used in shells and in the Ethiopian war as a spray from airplanes. Probably an attack on the civilian population would be in the latter form.

Mustard gas is also known as yperite (French) or yellow cross (German). It is known as mustard gas because of its odor and as yperite because the Germans first used it at Ypres in July, 1917. The term yellow cross is derived from the symbol used by the Germans to designate the shells containing this gas.

Mustard gas is a dark brown liquid (dichlorethylsulphide, | (C₂H₄Cl)₂S], with a high boiling point (214 degrees F.) and changes slowly into a colorless gas. This gas is one of the most difficult with which to cope because earth on which the oil has fallen remains permeated for from three days to a week. The length of time depends upon the weather. Rain neutralizes the soil within three days and dry weather permits the gas to remain potent for at least a week.

Eye casualties can occur (1) as a result of direct splashing of the oil into the eyes, (2) by direct transfer from the hands to the eyes after contact with the earth, clothing or other objects and (3) by vapors.

The latter is by far the most frequent.

The ocular symptoms following contact with the vapors of mustard gas occur only after four to six hours. Although the symptoms are severe there are no serious or permanent ocular lesions in the usual conditions of warfare, but if the eye is exposed to high concentrations the cornea can be severely damaged as experimental work has shown.

Hyperemia of the conjunctiva accompanied by tearing, photophobia and blepharospasm, appears approximately four to six hours after contact.

The pain becomes very severe about eight hours after exposure to the

gas and edema of the eyelids develops. The appearance is similar to that of infectious conjunctivitis. The eyelids are swollen and in attempting to separate them with the aid of a retractor, a cloudy fluid is expressed. The conjunctiva is red with marked chemosis. In severe cases, the lower fornix is red but the part of the conjunctiva exposed between the eyelids can be porcelain white. Corneal lesions are usually discrete, but epithelial desquamation may often be revealed by fluorescein. The exposed part of the eyes between the eyelids is most affected by the vapors.

If proper treatment is administered, and frequently without treatment, edema of the eyelids disappears in a few days. Hyperemia, photophobia and tearing still persist for a week or two. Blepharospasm and photophobia may be present even longer in severe cases.

When there is direct contact with the mustard oil the ocular lesions are much more severe with corneal ulcers and sometimes even with perforations of the cornea. The skin and eyelids may present first degree or even second degree burns.

Late Conjunctival Complications: The conjunctiva may remain very sensitive to all irritants (wind, dust, light, etc.) and attacks of blepharoconjunctivitis often occur. In exceptional cases epiphora caused by cicatricial obliteration of the lacrimal puncta has been noted. Symblepharon may develop in some cases. There may be abnormal vascularization characterized by the persistence of conjunctival vessels of carmine color. Biomicroscopically, true varices of the conjunctiva may be seen near the limbus years later.⁶

Late Corneal Complications: The cornea in most cases returns to normal. In others leukomas develop and recurrent ulcers of the cornea have been observed after several years. These serious and lasting corneal lesions may be seen especially if direct contact with the mustard oil (splash) has occurred or transfer by the fingers has been possible, but are rare if there has only been contact with the vapors of the gas.

Intra-ocular Complications: In severe mustard gas burns of the body, Beauvieux⁸ and Genet and Delord⁶ noted dilatation of the retinal veins and hyperemia of the disk. In his experimental work on monkeys Wessely⁹ also noted some retinal hemorrhages and he believed that they were due not to the general intoxication, but to the local penetration through the burned ocular tissues; such hemorrhages occurred only in those animals which had not had a protective ointment introduced in

their eyes prior to the instillation of mustard gas oil.

Prognosis: Generally the prognosis in cases of mustard gas burns is benign. Beauvieux⁸ observed only two cases in 1,800 mustard gas casualties in which severe corneal ulceration developed and even these regained useful vision.

Tissue which previously has been affected by mustard gas is susceptible to smaller concentrations of the vapor.¹⁰

Treatment of Mustard Gas Burns of the Eye: Although eyes that have been exposed to the vapors of mustard gas may at first look severely damaged, the prognosis is good and most cases will recover entirely even if no treatment is applied to the eyes. Especial care should be taken to avoid secondary infection and it is, therefore, better to apply no treatment at all if sterile solutions and drops are not available.

But if the eyes have been splashed by mustard gas oil, it is important to irrigate the eyes as soon as possible. The immediate and copious use of water, advised by Pellathy,¹¹ to lessen the action of mustard gas on the eyes because of the difficulty in obtaining proper solutions quickly, may well be the most important first aid treatment, and should be used as early as possible, preferably within fifteen minutes since most of the mustard gas has been absorbed by that time.

The patient should be assured that sight will be restored and if possible the eyelids should be separated permitting him to see. Pontocaine (½ per cent) should be instilled once or possibly twice if it is necessary to relieve pain or to temporarily separate the eyelids, but cocaine and atropine should be avoided. Ointments should not be used in the treatment of mustard gas injuries for the first few days until the chemical has been completely eliminated from the tissues since mustard gas is absorbed by any fatty substance and it is thus kept in contact with the eye. No dressing should be applied.

The eyes may be washed with alkaline solution (sodium bicarbonate to 5 per cent) or neutralizing solution (dichloramine-T). Dichloramine-T may be used in 0.5 per cent solution. It must be dissolved in an organic solvent (chlorinated paraffin or chlorinated diphenylether), and a local anesthetic should be instilled prior to irrigation. Hypertonic solutions* have been recommended because it is claimed they induce drainage by osmosis, thus hastening elimination of the gas. Livingston

Saturated aqueous solution of sodium sulphate 800 grams Simple syrup 200 grams

Magnesium sulphate Simple syrup Water

and Walker¹⁴ reported that saturation of the system with ascorbic acid, given intravenously in four rabbits, proved to have a remarkable effect in preventing the spread of keratitis and the progress of the eyelid inflammation resulting from mustard gas. However, Mann and Pullinger¹⁵ stated that intravenous injections of ascorbic acid neither prevent nor influence mustard gas lesions of the eyelids, conjunctiva or cornea. Pickard¹⁶ advised the external application of mercurial salve to the eyelids in order to prevent chalazia, hordeola, and small multiple abscesses of the eyelids. However, it seems better to use no antiseptics since all are irritating to the tissues and since, notwithstanding the appearance, there is no infection if the eye is properly treated.

During convalescence zinc or boric acid solution may be instilled. Tinted lenses may also be prescribed.

Experiments with Mustard Gas on Animals: Our experiments with rabbits*† have demonstrated that the ocular lesions are extremely severe if even the smallest amount of liquid mustard gas is applied to the cornea, and the tissues seldom heal with little scarring as reported by other workers, even if immediate or subsequent treatment is administered. The use of a 5 per cent sulfanilamide-sulfadiazine ointment (equal parts) applied three days after instilling liquid mustard gas does not retard healing and may tend to prevent or control secondary infection. However, we have not used dichloramine-T which Heinsius¹⁷ claims will prevent damage if the eye is flushed within the first fifteen minutes after mustard gas is applied.

Lewisite: Lewisite (Cl CH:CHAsCl₂) was prepared for use in the last war but was never liberated. It is a heavy, oily liquid, colorless in its pure state but dark upon standing. From experimental studies, its action is similar to that of mustard gas but more destructive. According to Hughes¹⁸ the onset of symptoms following contact either with the vapor of lewisite or the liquid is almost immediate. His experiments with rabbits showed that within an hour there is marked edema of the conjunctiva and a definite clouding of the cornea. After a few hours, necrosis of the conjunctival vessels with the formation of hemorrhagic area is quite striking and a marked fibrinous iritis develops. Hughes states that in general the subsequent course of the lewisite lesions shows more corneal edema, more intense vascularization of the cornea and

^{*} de Gara, P. F., Loutfallah, M. and Berens, C. under a grant from The Ophthalmological Foundation, Inc. and The John and Mary R. Markle Foundation, Inc. at Cornell University Medical School. † Mustard gas furnished through the courtesy of Dr. Kenneth C. Blanchard, Department of Biology, New York University.

more tendency to purulent exudation and corneal ulceration than is the case of mustard gas burns.

Treatment: The treatment is probably the same as for injuries caused by mustard gas but we have had no experience with it. The use of copious irrigations with water or a 1.5 per cent solution of sodium bicarbonate is recommended. Hughes¹⁸ states that except for the use of chlorinated solutions, the treatment of lewisite burns is essentially that of mustard gas. Hydrogen peroxide and potassium permanganate for the treatment of lewisite burns have been discarded generally.

LUNG IRRITATING GASES

Although the lung irritating gases are the most serious because of their lethal action, they are not so important from the standpoint of the ophthalmologist. However, these gases, which include chlorine, chloropicrin (CCl₃NO₂), and phosgene (COCl₂), are irritating to the eyes. Phosgene may be associated with intra-ocular hemorrhages which probably are secondary to the anoxemia resulting from pulmonary edema.⁵

STERNUTATORY (SNEEZING) GASES

The sternutatory gases are in reality solids of the arsine chemical group and include diphenylarsine [(C₆H₅)₂As], diphenylamine-chlorarsine (Adamsite), diphenylchlorarsine [(C₆H₅)₂AsCl], and diphenylcyanarsine [(C₆H₅)₂AsCN]. These chemical substances cause irritation of the eyes with excessive lacrimation. Sneezing is the essential symptom, but nausea and vomiting as well as severe headaches also occur.

The eye symptoms are usually of short duration and after a few minutes the effects have passed.

LACRIMATORY GASES

Lacrimatory gases include chloracetophenone* (C₆H₅COCH₂Cl) (a white crystalline solid), benzyl bromide (C₆H₅.CH₂Br)[†], chloro-acetone (CH₃.COC₆H₄Cl)[†] and bromacetone (Br.CH₂CO.CH₃)[†]. The ocular symptoms resulting from the use of lacrimatory gases are: burning pain, excessive lacrimation, injection of the conjunctiva and photophobia and in rare cases, when the gas is splashed into the eyes, free exfoliation of the epithelial covering of the cornea. Itching, burning,

^{*} Common tear gas used in police work.

[†] These last three chemicals are in liquid form.

tearing, blepharospasm and photophobia are so intense that those affected are incapable of finding their way without aid. The bulbar and palpebral conjunctivas are markedly hyperemic but there is no ciliary injection. These symptoms appear immediately after exposure to the gas and disappear within a few minutes or hours, leaving no trace except when splashed into the eyes; then the burn is similar to that produced by strong acids.

Prognosis: So far as the eye is concerned, lesions produced by lacrimatory gases are benign unless the liquid is splashed into the eye. Schmidt¹⁹ reported a case in which tear gas (brommethylethyl ketone), which is generally considered harmless and to cause only transient irritation, was shot into an eye and produced severe destruction and permanent damage deep in the orbital tissues.

TREATMENT OF INJURIES CAUSED BY LUNG IRRITATING, STERNUTATORY AND LACRIMATORY GASES

The patient should be removed from the contaminated area. Even if nothing is done all eye symptoms usually disappear rapidly. Therefore, useless treatments which may cause infection if nonsterile solutions are used should be avoided. If warm sterile solutions are available the eyes should be flushed, e.g., with sodium chloride 1.4 per cent, sodium bicarbonate 2 to 5 per cent or boric acid 2 per cent. Sodium sulfite has been recommended by McNally*5 to neutralize and dissolve lacrimatory gases. If pain is severe a sterile solution of pontocaine (½ per cent) may be instilled once or twice; if irritation persists light liquid petrolatum may be instilled.

If liquid was splashed into the eye immediate irrigation is necessary. Water should be used if no other sterile or nonirritating solution is available.

Systemic Toxic Gases

The systemic toxic gases include hydrocyanic acid, cyanogen chloride and cyanogen bromide. These gases are usually fatal in a few seconds or at most minutes. However, there are rare examples of blurring of vision and irritation of the eyes in exceptional cases surviving such an attack.

^{*} Sodium sulfite 0.4 gm. Water 25.0 cc. Glycerin 75.0 cc.

Carbon monoxide is not used in chemical warfare but great quantities of it are produced when a shell explodes or when a machine gun or a cannon is fired. Intoxication can, therefore, be observed in badly ventilated dugouts or pill boxes.

OTHER CHEMICALS THAT MAY AFFECT THE EYES AS A RESULT OF TOTAL WAR

In addition to the gases from bombs or those that may be sprayed, civilians and workers may be exposed to a great number of chemicals. If bombs fall in the kitchen or in the shop, these chemicals may easily affect the victims' eyes. These substances which are the same as those encountered in industrial casualties may cause severe eye injury.

For example, caustic soda and caustic potash lyes as well as other alkalies produce lesions of the conjunctiva and cornea. Metal workers, rubber workers and chemical workers are especially exposed to these agents. Acrolein and ammonia used in refrigerating plants and in refrigerators are important because of the severity of the eye injury when there is direct contact, e.g., necrosis of the cornea. Battery acid is another hazard which might have to be considered in addition to sulphuric, nitric and other acids which cause severe burns of the conjunctiva, cornea and eyelids.

Acid Burns: Acid burns may cause immediate injury to the conjunctiva and cornea. The prognosis depends upon the amount and concentration of acid contacting the eye, and how long it acted.

Alkali Burns: Alkali burns may cause progressive injury of the eye. Strong solutions penetrate the cornea in a few minutes causing desquamation. Dense opacities follow with pannus. Penetrating ulcer of the cornea may be a sequela.

Immediate First-Aid Treatment of All Chemical Burns: The conjunctiva is flushed. The urgency of immediate treatment does not permit a special solution being made up. Therefore, the eyes should be flushed with water and a sterile nonirritating oil (liquid petrolatum) instilled, if available. The patient should then be referred to a specialist for appropriate treatment, for example, atropine for iritis, cauterization for corneal ulcers.

Special Treatment of Acid Burns: A solution of sodium bicarbonate (2 per cent) effectively neutralizes corrosive acids. Subsequent treatment depends upon the individual symptoms encountered. The follow-

ing have been recommended: boric acid ointment and an eye pad, liquid paraffin, cod liver oil, and mild silver protein (10 per cent) followed by a 2 per cent solution of boric acid.

Special Treatment of Alkali Burns: Treatment includes flushing the eye with water, saline solution (1.4 per cent) or boric acid (2 per cent). The instillation of an isotonic acetate buffer solution* neutralizes any excess alkali. Further treatment may include: atropine sulfate, 1 per cent solution, three times a day to control secondary iritis and breaking adhesions between the eyelids and eyeball by means of a glass or plastic spatula and boric acid ointment passed into the upper and lower conjunctival culs-de-sac twice a day. Secondary infection may be prevented or combatted by the instillation of a mild silver protein (10 per cent) followed by irrigation with saline solution (1.4 per cent) or the application of sulfadiazine ointment (3.5 per cent). The immediate application of rabbit peritoneum has been recommended by Brown²⁰ as a protective membrane to separate the cornea from the burned palpebral conjunctiva following most corrosive chemical burns.

At a later date, the excision of superficial corneal scars or keratoplasty may be required to restore vision when the corneal scars obstruct the pupil. If adhesions form between the conjunctiva and the eyeball (symblepharon) conjunctivoplasty may be indicated. If secondary glaucoma develops it is difficult to control and may require the injection of alcohol into the ciliary ganglion. If useful vision may be restored 1 cc. of 40 per cent alcohol may be injected into the ganglion after 1 cc. of novocain (2 per cent solution) has been injected and the needle left in place. If vision is destroyed, 80 per cent alcohol (1 cc.) may be injected.

Lime burns should receive continued treatment until all danger of cicatricial contraction of the conjunctiva and secondary opacification of the cornea is past. This type of injury tends to involve the deeper layers of the cornea and sclera, even when the eye appears to be only slightly affected, causing an associated iritis.

COMPLICATIONS OF BURNS CAUSED BY ACIDS AND ALKALIES

Complications which must be looked for and if possible prevented

Acetic acid 2.5 gm.
Sodium acetate 3.0 gm.
Sodium chloride 4.5 gm.
Distilled water 1000.0 cc.

[†] Sodium sulfadiazine in aquaphor 3.5 per cent

are: corneal ulcers, iritis, glaucoma and adhesions between the conjunctiva and the eyeball.

SUMMARY AND CONCLUSIONS

Although vesicant, lung irritating, sternutatory and lacrimatory gases are expected to cause casualties, physicians must be prepared for new unknown gases. For example, arsenated hydrogen, a hemolytic gas, was considered a possibility in the fall of 1939.

Physicians are urged to remember that applying no local eye treatment will usually do less harm than using medication which may damage the eyes or solutions or instruments that are not sterile, as secondary infection is the principal danger from the external application of the war gases.

The immediate treatment of all gas and chemical injuries of the eyes is to flush the conjunctival culs-de-sac with water or a sterile solution of salt (1.4 per cent). If acid is known to have caused the burn, sodium bicarbonate (2 per cent solution) should be used. If an alkali, the conjunctival culs-de-sac should be flushed with boric acid (2 per cent solution). The immediate instillation of light liquid petrolatum is useful and contraindicated only in mustard burns. Severe pain may be controlled by instilling pontocaine (0.5 per cent solution) or butyn (1 per cent solution) once or twice but it is preferable to control pain with internal medication (morphine, allonal, etc.) as most local anesthetics have a deleterious effect on the corneal epithelium. Secondary infection should be combatted with mild silver protein or sulfadiazine solution or ointment (3.5 per cent). Iritis should be suspected in all severe burns and treated with atropine solution or ointment unless secondary glaucoma develops. Ulcers of the cornea and the secondary corneal scarring also symblepharon may require surgical treatment.

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Dr. Harris was consulting otolaryngologist to the New York Post-Graduate Hospital and at one time served as professor of diseases of nose and throat at the New York Post-Graduate Medical School. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, and a member of

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Dr. Lichtwitz was professor of clinical medicine at Columbia University for the last eight years and chief of the medical division at the Montefiore Hospital for ten years. Prior to his coming to the United States in 1933, he was for two years on the staff of the Rudolf Virchow Hospital in Berlin, and from 1917 to 1931 he was director of the City Hospital in Hamburg. He was a former president of the German Society for Internal Medicine, an officer of the German Society for Gastroenterology and Metabolic Diseases and an officer of the Society for Internal Medicine, Berlin.

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Paulsen, Alice Elizabeth: 15 Merrian Avenue, Bronxville, New York; born in New York City, February 15, 1890; died in Hillside, New York, March 16, 1943; received the degree of Ph.D. from Columbia University in 1924; elected an Associate Fellow of the Academy February 3, 1927; and served in research from 1927 to 1937 with the Committee on Public Health Relations.

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Dr. Steiner was consulting physician to the Hartford Hospital since 1934, and chairman of the medical and surgical staff from 1925 to 1933, having joined that institution in 1901 and serving in numerous capacities. He was also consulting physician to the Hartford Orphan Asylum, Bristol, New Britain General, Meriden, Middlesex (Middleton) and the Charlotte Hungerford hospitals, Torrington, and honorary physician to the Manchester Memorial Hospital.

Dr. Steiner was a Fellow of the American College of Physicians, a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and, except for a few sessions, a member of the House of Delegates from 1919 to 1940, a member of the American Association of Pathologists and Bucteriologists, and a member of the Association of American Physicians, American Clinical and Climatological Association and its president from 1934 to 1935, Medical Library Association and its president from 1931 to 1933, American Association of the History of Medicine and its president from 1937 to 1939, Congress of American Physicians and Surgeons and its secretary from 1911 to 1932, and the Connecticut State Medical Society, as its secretary from 1905 to 1912, chairman of its council from 1929 to 1933, and its president from 1934 to 1935.

In 1937 the Hartford Medical Society, which he served as Librarian from 1903 to 1941 and president in 1929, named its Library the Walter R. Steiner Medical Library in his honor.

Dr. Steiner made numerous contributions to literature on internal medicine, pathology and medical history.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



JUNE, 1943

SURGICAL METHODS FOR RELIEF OF PAIN*

Francis C. Grant

Professor of Neurosurgery, University of Pennsylvania School of Medicine

Problem 1 and its relief is a chief cause for the development of medicine. Drugs, opium and alcohol, were the first reliance of the physician. Gradually, as knowledge increased of the sensory pathways along peripheral nerves and in the central nervous system, surgeons were called upon to relieve pain by section of these fibers. But surgical section of pain pathways has disadvantages. Most peripheral nerves carry both sensory and motor fibers; their severance causes motor paralysis as well as anesthesia. Section of the posterior roots of the spinal cord produces a complete loss of all modalities of sensation, touch, pain and most important, muscle sense. If the posterior roots leading to an extremity are sectioned, the resulting loss of sense of position produces a disability as crippling as that which follows motor paralysis. But this particular disadvantage was overcome by the careful clinical observation of Spiller who showed that the antero-lateral columns in the spinal cord carried only pain and temperature fibers. If this tract is sectioned the contralateral half of the body is rendered analgesic without the loss of function consequent upon interference with touch and muscle sense. The

^{*} Read October 19, 1942 at the fifteenth Graduate Fortnight of The New York Academy of Medicine.

incision into the cord is made with greatest safety and operative convenience at the level of the first thoracic segment. By this procedure pain referred to any area below the level of the ensiform cartilage can be relieved. Pain in the face is abolished by section of the sensory root of the trigeminal; pain in the tonsil and throat by severance of the trigeminal and glossopharyngeal nerves; pain in the neck and shoulders responds well to rhizotomy of the upper four or five cervical posterior roots, since the function of position sense in the muscles in the areas supplied by these nerves is relatively of little importance. But pain referred to the axilla, upper arm, forearm, and fingers is still a problem. Brachial plexus section or rhizotomy of the lower cervical and top thoracic posterior roots produces practical paralysis of the corresponding arm due to complete loss of muscle sense, and, incidentally, is not very effective in checking the pain. High cervical cordotomy at the level of the second cervical segment can be performed, but the neurosurgeon should keep in mind the possibility of phrenic paralysis. Recently section of the major pain pathways in the medulla and in the internal capsule have been suggested and successfully carried out to produce complete hemianalgesia. That such hitherto inaccessible sensory pathways should have been singled out for attack is evidence that the problem of unbearable pain cries out for solution.

In the clinic with which I am connected much contact has been had with pain since Drs. Spiller and Frazier2 between them worked out the technique for preganglionic section of the sensory root of the trigeminal and for section of the antero-lateral columns of the spinal cord. Trigeminal neuralgia was our first problem. This has been solved by cutting the outer four-fifths of the sensory root preferably through the temporal fossa. We speak of the solution of this problem, but it has not really been solved. Root section will relieve the paroxysmal and devastating pain in the face. Nevertheless about 5 per cent of these patients develop a burning paresthesia in the anesthetic area of the face and are even more miserable following operation than before since the burning pain is persistent. For this reason we were greatly interested in Sjökvist's report on section of the descending root of the trigeminal in the medulla. He claimed that section of this descending root would sever only pain fibers, leaves touch sensation undisturbed and thus spares the patient the subjective sensation of sensory loss. Weinberger3 in this clinic modified the Sjökvist4 technique in such a way as to avoid injury

to the restiform body and thus reduce postoperative neurologic sequellae to a minimum. By this procedure pain in the face can be abolished with but the slightest objective and no subjective loss of touch sensation.

But medullary tractotomy is not a suitable procedure for routine use. Sufferers from major trigeminal neuralgia are elderly, many hypertensive and feeble. Medullary tractotomy requires a general anesthesia given in the prone position. Local anesthesia cannot be used since medullary section is painful and a sudden movement of the patient at the time of this incision might result in disaster. The cerebellar tonsil and posterior inferior cerebellar artery require retraction. The landmarks for the medullary incision are not of the best. That part of the descending root carrying fibers to the third division lies most centrally in the medulla. The mandibular area is commonly involved in trigeminal pain. Therefore, to be certain to section these fibers the medulla must always be deeply incised. Ten cases of true trigeminal neuralgia have been operated by this technique without mortality or permanent neurologic sequellae but with complete relief of pain in only eight. Since trigeminal neuralgia is not a lethal disease, any operative procedure used in its relief must be the simplest and safest available. By the subtemporal approach the mortality does not exceed 1.8 per cent. The potentialities for disaster in any suboccipital approach are much greater than in the subtemporal. Medullary tractotomy has, therefore, been abandoned as a routine procedure in the relief of major trigeminal neuralgia.

Although a number of leading neurosurgeons are not of this opinion, we have for a long time appreciated the value of alcohol injection as an initial step in the treatment of trigeminal neuralgia. It is of importance in differential diagnosis. Furthermore, an alcohol injection accustoms the patient to the sensation of complete anesthesia in the face. When after a year or longer his anesthesia disappears and his pain returns, he is entirely cognizant of how his face will feel after his root has been cut. He accepts his permanent anesthesia much more readily if he knows by experience just what abnormal sensations he must expect in return for complete relief of pain. Seventy-eight per cent of the cases in our records complaining bitterly of postoperative paresthesias were subjected to root section as a primary procedure without preliminary preparation by alcohol injection. Nerve block is painful and not consistently successful. But, nevertheless, it should always be attempted before per-

TABLE 1
CANCER OF MAXILLARY ANTRUM AND UPPER JAW

| | Cases | |
|---|---|----|
| | Pain relieved | 38 |
| ` | Pain partially relieved Pain not relieved | 9 |
| | Died | 8 |
| | | 3 |
| | Total | 58 |
| | | |

| TREATMENT | | RESULTS | NO. OF CASES |
|---|--------------------------|--|-----------------|
| | 2nd Division | Pain relieved Pain not relieved | 15 6 |
| Alcohol injection | 3rd Division | Pain relieved Pain not relieved | 3 2 |
| | 2nd and 3rd Divisions | Pain relieved Pain 60% relieved | 7 6 |
| Intracranial neurectomy, 2nd and 3rd Divisions | | Pain relieved Pain 75% relieved Died | 5 3 1 |
| Avulsion of sensory root | | Pain relieved Died | 8 2 |

manent anesthesia is produced by root section.

Cancer is only too frequently accompanied by intractable pain. Should reliance be placed on morphine and its derivatives to allay suffering, or should an attempt be made to relieve the pain by blocking afferent pathways leading from the involved area? The pain from cancer is constant and harrowing, without surcease by night or day. Relief afforded by morphine is intermittent; pain ceases when the drug takes hold, then reappears. The patient bears with it as long as he can, then begs for more morphine. But section of afferent pathways, carefully planned and properly performed, can result in complete and permanent relief of pain.

Unfortunately, however, the problem is not as simple as it seems. The methods at one's disposal for the relief of pain are not completely satisfactory. Cordotomy, rhizotomy, section of the branches or the sensory root of the trigeminal nerve, or injection of alcohol into the spinal

TABLE II

CANCER OF ETHMOID AND SPHENOID SINUSES: CHEEK AND SKIN

| Ethmoid and Sphenoid Sinuses | Cases |
|------------------------------|-------|
| Pain relieved | 2 |
| Pain partially relieved, | 2 |
| Pain not relieved | 3 |
| | |
| Total | au |

| TFEATMENT | | PLSULTS | NO, OF CASES |
|--------------------------|-------------------|---------------------|-----------------|
| Alcohol injection | 2nd Division | Pain relieved | 1 |
| , | 5th cranial nerve | Pain not relieved | 3 |
| Avulsion of sensory roof | | Pain relieved | 1 |
| Fifth nerve | | Pain 60% relieved | 1 |
| | | Pain not relieve | 1 |
| ! | Cheek, skin | | 21 |
| j | | Pain relieved 19 | } |
| | | Pain not relieved 3 | |
| | | Died 2 | |
| Alcohol injection | 2nd Division | Pain relieved | 7 |
| · | | Pain not relieved | 2 |
| | 2nd and 3rd | Pain relieved | 4 |
| | Division | Pain not relieved | i - |
| Intracranical neurectomy | | | |
| 2nd and 3rd Divisions | | Pain relieved | 1- |
| Avulsion of sensory root | f | Pain relieved | 1 |
| 5th nerve | | Died | 2 |

subarachnoid space all involve the patient in definite hazards. Cordotomy, rhizotomy, or section of the trigeminal root imply a major surgical operation with its attendant risks in persons already debilitated by malignant disease. The antero-lateral columns lie adjacent to the pyramidal tracts. A badly placed incision in the cord can result in motor weakness in the extremities. Furthermore, bilateral cordotomy is followed in at least 10 per cent of cases by urinary retention, temporary or permanent. Rhizotomy causes complete loss of all modalities of sensation. If it is performed for pain in the arm due to involvement of the brachial plexus consequent on metastasis from mammary cancer, the arm and hand are rendered useless, for, although they can be moved, no

TABLE III
CANCER OF MANDIBLE

| | Cases |
|-------------------|-------|
| Pain relieved | 25 |
| Pain not relieved | 9 |
| Died | 3 |
| Total | 37 |

| TREATMENT | | RESULTS | NO. OF CASES |
|--------------------------|---------------------------------------|------------------------------------|-----------------|
| Alcohol Injection | 3rd Division | Pain relieved Pain not relieved | 11 6 |
| | Inferior dental and lingual nerves | Pain not relieved | 1 |
| | 2nd and 3rd | Pain relieved | 6 |
| | Divisions | Pain not relieved | 2 |
| Avulsion of sensory root | | Pain relieved | 8 |
| | | Died | 3 |

sense of their position remains. Subarachnoid injection of alcohol may paralyze motor as well as sensory nerves and cause urinary retention or weakness in the lower extremities.

The problem of relief of pain is further complicated by the spread of the cancer with the involvement of afferent pathways adjacent to those severed. A uterine or prostatic cancer may cause intense pain in one flank or down one leg. A unilateral cordotomy or subarachnoid alcohol block may give relief for two or three months. Then, as the growth spreads, equally severe distress may appear on the opposite side.

From the practical standpoint, therefore, the decision to attempt to relieve pain by blocking afferent pathways must rest on a number of factors: the position and rapidity of growth of the cancer; the probable period of life expectancy of the patient; the amount and location of the pain; the patient's reaction to it, and the dosage of opium necessary for its control. Finally, the patient's general condition as an operative risk requires careful consideration before radical surgical intervention is proposed. Roentgenograms of the chest should always be taken to determine the presence or absence of pulmonary metastases. If the lungs

Table IV

CANCER OF CHEEK, MUCOUS MEMBRANE AND TONGUE

| Check, Mucous Membrane | Cases |
|-------------------------|-------|
| Pain relieved | 7 |
| Pain partially relieved | 3 |
| Pain not relieved | 2 |
| | |
| Total | 12 |

| TP1 VIMENT | | ri sults | NO, OF CASES |
|-------------------|---------------------------------------|---------------------------|-----------------|
| Alcohol injection | 2nd Division | Pain relieved | 7 |
| · | | Pain 50% relieved | 3 |
| | | Pain not relieved | 2 |
| | Tongue | | 21 |
| | | Pain relieved 12 | |
| | | Pain partially relieved 6 | |
| | | Pain not relieved 3 | |
| Treatment | | | |
| Alcohol injection | 3rd Division | Pain relieved | 9 |
| • | | Pain partially relieved | 4 |
| | | Pain not relieved | 2 |
| | Inferior dental and lingual nerves | Pain partially relieved | 2 |
| | 2nd and 3rd | Pain relieved | 3 |
| | Divisions | Pain not relieved | 1 |

are involved, or if the sufferer's general physical condition suggests a life expectancy of less than three months, radical surgical intervention should not be attempted unless the pain is devastating. Under such conditions an attempt to block afferent pathways by the injection of alcohol into the subarachnoid space or further recourse to morphine is indicated.

Our purpose is to show what can be done for relief of pain by interruption of sensory pathways, the hazards involved, and what justification exists for suggesting these procedures rather than continuing with morphine or dilaudid hydrochloride sedation. Three groups of patients have been selected: those with pain in the face, jaw, mouth and sinuses with or without metastases to the cervical glands; those with pain in the arm from mammary cancer or axillary or supraclavicular metastases

TABLE V
CANCER OF BASE OF TONGUE, TONSIL AND NECK

| Base of Tongue and Tonsil | | | |
|-------------------------------|----------------|---------------------------|--------|
| Pain relieved | | Cases | |
| Pain partially reli | a | 21 9 | |
| Pain not relieved | eved | | |
| Died Peneven | | 17 | |
| , | | 3 | |
| | Total | | |
| Neck | Total | 50 | |
| Pain relieved | | | |
| Pain partially 1cl | ieved | 7 | |
| - mar partially for | icvett | 2 | |
| Total | | 9 | |
| TREATMENT | | RESULTS | NO. OF |
| | | | |
| Alcohol injection 3rd | Division | Pain not relieved | 15 |
| | | Pain partially relieved | 8 |
| Avulsion of sensory root | | | |
| neutron of sensory 1000 | | Pain relieved | 8 |
| | \ | Pain partially relieved | 1 |
| | ļ | Pain not relieved Died | 2 |
| Avulsion of 5th and 9th nerv | 00 | Dieti | 1 |
| on and oth here | | Pain relieved | 13 |
| | | Died | 2 |
| Cervical rhizotomy; posterior | cervical roots | Pain relieved | 7 |
| of 1st to 5th cranial nerves | 1 | Pain partially relieved | 2 |

involving the brachial plexus; and lastly a group with abdominal or pelvic disease producing pain anywhere below the ensiform process.

In the first group the afferent pathways involved comprise the trigeminal and glossopharyngeal nerves and the upper four or five cervical posterior roots. Cancer about the face is a common and, at times, distressingly painful condition. The simplest problem to handle is those cancers lying within the sensory distribution of the trigeminal. Alcohol block of the appropriate branch should always first be attempted. But, that the malignancy, especially when it involves the maxillary antrum, ethmoid or sphenoid, may displace the second division from its usual anatomic position, thus making accurate injection difficult or impossible, must be kept in mind. Those cancers lying within the sensory field of the second division are most effectively relieved, because a block of all three divisions by root section gives a wide area of anesthesia about the growth into which the malignancy can spread without producing more

 $$T_{\mathrm{VBLE}}$$ VI analysis of results after cordotomy for relief of pain

| | Cordo | tomies |
|---|------------------------|--------------------------|
| 126 patients (58 women, 68 men) Bilateral cordotomy Unilateral cordotomy | - | 31 56 70 |
| | Number | Per Cent |
| Completely relieved 75% relieved (8 recurrences opposite side) 50% relieved (6 recurrences opposite side) Not relieved Died | 80 19 9 5 | 61 15 7 4 10 |

pain. When the pain is referred to the tongue or floor of the mouth, a third division block is indicated. If it is not completely successful, the superficial cervical roots may be dissected out and sectioned where they swing forward over the sternocleidomastoid muscle. If an alcohol block is unsuccessful. sensory root section or preganglionic section of the second and third divisions can be carried out by the subtemporal approach, a simple procedure readily performed under local anesthesia alone. Pain in the base of the tongue, tonsil or throat indicates ninth nerve involvement. The easiest way to section the glossopharyngeal is by a unilateral suboccipital craniectomy. A short extension downward permits exposure of the upper three cervical roots. With the medulla thus widely exposed, a tractotomy on the descending root of the trigeminal is to be preferred to root section at the pons. In our experience tractotomy is easier and just as satisfactory in producing relief as root section. This is the most effective use for tractotomy, and its value has been repeatedly proven. The only referred pain above the clavicles which cannot be relieved by one or more of these maneuvers is that deep in the ear. Fortunately such pain is uncommon. Three patients with cancer of the tonsillar pillars had such complaint. In one patient the fifth, seventh, eighth, ninth and twelfth nerves together with the upper three cervical posterior roots were sectioned without the slightest relief of this pain.

When a mammary cancer or a pulmonary sulcus tumor spreads to

TABLE VII
SUMMARY OF TYPES OF PAINFUL LESIONS REQUIRING CORDOTOMY

| No. of Cases |
|-----------------|
| 71 |
| 26 |
| 4 |
| 2 |
| 20 |
| _ |

invade the brachial plexus, intense pain in the shoulder, arm, forearm or hand results. The answer to this problem might seem easy, section of the posterior roots from the third cervical to the first thoracic segments. This can be done, but the arm and hand are useless since all modalities of sensation are lost. Furthermore, the useless insensitive arm is heavy and drags on the shoulder, causing added discomfort. Rhizotomy is not a satisfactory answer to this problem in most cases. The alternatives are high cervical cordotomy, section of the pain fibers in the medulla, or in the cerebral crus. Four high cervical cordotomies at the level of the second or third cervical segment have been carried out, two combined with posterior root section from the fourth to the seventh cervical segments. One cordotomy and one combined cordotomy and root section were successful, the other two failed to relieve the pain effectively. If the eighth cervical and first thoracic posterior roots are spared, enough sense of position remains in the fingers to allow some use of the hand and fingers. A cordotomy at the second cervical segment should eliminate all pain below the fifth or sixth cervical distribution. But cordotomy plus rhizotomy is a more extensive and therefore more dangerous procedure than a simple cordotomy. We have had no experience with section of the pain fibers in the medulla as described by Schwartz and O'Leary⁵ and J. C. White.⁶ In a single case the sensory pathways were cut in the crus with fortunately complete relief of pain, although the subsequent sensory examinations showed that we had not followed Walker's technique with accuracy.

Pain referred to any area below the ensiform cartilage can be re-

Table VIII
COMPLICATIONS AFTER BILATERAL CORDOTOMY

| | | No. of Cases |
|---|-----------------|-----------------|
| Vomiting | | 15 |
| Distention | | 17 |
| Retention of urine (Eight patients had cancer of bladder, four had subarachnoid alcohol injection) | previous | 26 |
| Motor weakness | | 10 |
| Died Meningitis Shock Cachevia | 2 2 4 | 8 |

lieved by cordotomy at or just above the level of the first thoracic segment. It is important to cut the antero-lateral tracts at this level because it is above the point at which the sympathetic fibers enter the cord. If any doubt exists as to the proper level for section, a carefully induced spinal anesthesia with accurate observation as to the level to which the anesthesia must be carried to produce relief of pain is valuable. This test is especially important when an attempt is to be made to relieve the pain of tabetic crises. Cordotomy, whether uni- or bilateral, can be carried out under local anesthesia, since section of the anterolateral tracts is not in itself painful. Local anesthesia permits of testing of the level of analgesia as the tracts are incised. Once an adequate level to include the area to which the pain is referred has been reached, no further incision into the cord is necessary. In this way any damage to adjacent pyramidal tracts can be avoided. A bilateral section should be done in the same way, but the two incisions should never be made at the same level. Usually one incision is made at cervical eight or thoracic one, and the opposite tract cut at thoracic three or four. If both columns are cut in the same segment, a complete transverse myelitis may result. The dangers accompanying cordotomy are involvement of the lateral pyramidal tracts with consequent motor weakness or of the anterior pyramidal pathways resulting in sphincteric disturbances.

Why cordotomy, why not inject alcohol into the subarachnoid

TABLE IX
COMPLICATIONS AFTER UNILATERAL CORDOTOMY

| | | No. of Cases |
|---|------------|-----------------|
| Vomiting | | 5 |
| Distention | | 5 |
| Retention of urine (Three had cancer of prostate. Three had previous suba chnoid alcohol injection) | ra- | 8 |
| Motor weakness (Two had previous subarachnoid alcohol injection) | | 6 |
| Died Cachexia Pneumonia | 3 2 | 5 |

TABLE X
RESULTS WITH INJECTION OF ALCOHOL INTO THE SUBARACHNOID SPACE

| | Number of Patients | Per Cent |
|--|-----------------------|----------|
| Total patients | 31 | |
| Relief of pain | 15 | 50 |
| Partial relief of pain | 6 | 20 |
| No relief of pain | 10 | 30 |
| Hemiparesis after injection | 1 | |
| Paralysis of legs and sphincters after injection | 1 | |

space as suggested by Dogliotti?⁸ A number of alcohol injections have been done. The results have been satisfactory, considering the easy technique demanded by this procedure. No question exists but that this is an effective means for relieving pain. But we are not impressed with this procedure. Many patients have been seen in whom alcohol was injected in other clinics and who have come for further relief. The chief objection to alcohol is that its effect is uncertain and uncontrolled. Furthermore, if alcohol is ineffective in relieving pain it may still destroy

the fibers to the sphincters on one side. If now a unilateral cordotomy is necessary, the pathways governing sphincter control on the opposite side are implicated and retention may result. Loss of sphincter control should never follow a unilateral cordotomy unless the bladder is already involved by the malignancy. In our opinion a unilateral cordotomy carried out through a hemilaminectomy under local anesthesia is almost as safe and much more likely to result in complete relief of pain, and is accompanied by less chance of untoward complications than is the injection of alcohol into the lumbar subarachnoid space.

Severe pain in many areas of the body can be relieved, at a price. The pain of trigeminal neuralgia at the price of anesthesia of the face and the remote chance of a persistent paresthesia in the anesthetic zone. The pain of cancer can be relieved—at a price, the price of an operative procedure, loss of sensation, possible motor weakness and sphincteric disturbance. The question becomes, therefore, one of expediency. Is the pain sufficiently severe to advise the patient that the price he may have to pay for relief is not too high? If our experiences with this problem have helped to answer this question, this paper has served its purpose.

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EFFECT OF VITAMIN E THERAPY ON THE CENTRAL NERVOUS SYSTEM IN AMYOTROPHIC LATERAL SCLEROSIS*

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trophic lateral sclerosis is not amenable to any form of treatment. Wechsler,¹ on the basis of experimental studies of animals that were deprived of Vitamin E and which developed paralysis and atrophies (Ringsted,² Lipshutz,³ Burr, Brown and Moseley,⁴ Einarson and Ringsted⁵), believed that patients suffering from amyotrophic lateral sclerosis might respond to a synthetic preparation containing alpha tocopherol. Wechsler,¹ Rosenberger,⁶ and Bicknell¹ found that alpha tocopherol and natural Vitamin E act favorably in some cases of amyotrophic lateral sclerosis and bring about varying degrees of improvement, perhaps in inverse ratio to the age and duration of the disease. Doyle and Merritt,⁶ Denker and Scheinman⁰ and Ferrebee, Klingman and Frantz,¹⁰ however, using the same form of treatment were unable to produce improvement or to arrest the course of the illness in patients with amyotrophic lateral sclerosis.

A number of cases of amyotrophic lateral sclerosis were treated at the Montefiore Hospital with Vitamin E and alpha tocopherol. Ten of these cases came to necropsy and except for one, none responded clinically to this form of treatment. The age, duration of the illness, and the fact that they may not have been treated adequately may be used as arguments against the lack of improvement. In this presentation, emphasis will be placed on the possible influence of this form of treatment on the affected structures of the central nervous system and not on the clinical results. The ten cases of amyotrophic lateral sclerosis that received Vitamin E were investigated histopathologically and compared with material from about forty untreated cases. As will be demon-

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strated, in many of the treated cases, the destruction of myelin sheaths and axis cylinders was less intense than in the untreated cases, while the dense gliosis which is usually present in amyotrophic lateral sclerosis, was diminished or almost absent in those that received Vitamin E. The anterior horn cells and the nerve cells of the involved bulbar nuclei remained unchanged and showed no signs of reversibility.

METHODS OF PROCEDURE

Ten cases (Tables I and II) of amyotrophic lateral sclerosis that received Vitamin E in the form of ephynal, alpha tocopherol, a diet rich in Vitamin E, thiamine chloride, wholewheat germ oil and bile salts form the basis of this presentation. Two patients received ephynal by mouth without intramuscular injections of alpha tocopherol. The treatment in the other eight cases conformed to that outlined by Wechsler.¹

Sections from various cortical areas (where available), internal capsule, peduncles, pons, medulla oblongata and spinal cord were embedded in parlodion and stained by the myelin sheath and cresyl violet methods. Frozen sections were stained by the myelin sheath, Bielschowsky, Sudan III and Holzer methods. For purposes of comparison the gliosis in the untreated cases was designated as dense while in the treated cases there were gradations which were divided into moderate, slight or very slight gliosis. Brief clinical and histopathological reports pertaining only to the specific problem will be given.

REPORT OF CASES

 CASES TREATED WITH VITAMIN E INCLUDING ALPHA TOCOPHEROL INTRAMIUSCULARLY, SHOWING SIGNIFICANT CHANGES

IN THE INVOLVED PATHWAYS.

CASE 1—F.E., a man, aged 64, was admitted to this hospital on December 16, 1939 with a history of difficulty in pronouncing consonants since February 1939 followed later by choking episodes while swallowing, regurgitation of food through the nose, dyspnea on exertion and spontaneous laughing and crying. The speech became more indistinct. Later, there appeared fibrillations of muscles of the arms and legs, sial-orrhea and progressive weakness of the upper and lower extremities.

Neurological examination disclosed: atrophy, moderate weakness and fibrillations of the muscles of the shoulder, arm and hand; hyper-

TABLE I

CASES TREATED WITH VITAMIN E INCLUDING ALPHA
TOCOPHEROL INTRAMUSCULARLY SHOWING SIGNIFICANT
CHANGES IN THE INVOLVED PATHWAYS

| Patient | Sex | Age | Duration of Illness | Treatment with alpha toco-pherol | Histologic Picture |
|---------|-----|-----|---------------------------|--|---|
| 1 | M | 64 | 1 yr., 10 mo. | 7½ months. | Myelin sheath—No demyelinization noted. H.P.—Slight changes—insular. Bielschowsky—slight changes. Fat—None. Holzer—very faint gliosis—insular. |
| 2 | M | 60 | 2 yrs., 7 mo. | 1 month and 4 days. | M.S.—faint demyelinization with small islands of myelin sheath swelling and destruction. Axis cylinders slightly less than in ordinary cases. Holzer—faint gliosis. |
| .3 | М | 44 | 6 yrs. | 4 months and 5 days. Treated intensively. | M.S.—hardly any pallor. H.P.—slight disintegration of fibers—insular. Bielschowsky — slight disintegration. Fat—present—not as much as in ordinary cases. Holzer—slight gliosis—insular., |
| 4 | F | 53 | 1½ yrs. | 7 months and 3 weeks. | M.S.—no visible demyelinization. H.P.—slight disintegration of fibers—insular. Bielschowsky — silght disintegration. Fat—none. Holzer—faint gliosis—insular. |
| 5 | F | 70 | 1 yr., 1 mo. | 2 months and 7 days. | M.S.—very slight demyelinization. H.P.—slight changes—insular Fat—very little. Bielschowsky—slight changes. Holzer—faint gliosis—insular. |
| 6 | M | 54 | 2 yrs. | 5 weeks and 3 days. Received treatment also on the outside, but could not determine exact amount. This patient showed slight improvement in neurological symptoms. | H.P.—destruction, however, not as marked as in average case; more marked on the right. Fat—same as in ordinary cases. Bielschowsky—destruction, but less than in ordinary cases, especially on the right. Holzer—moderate gliosis in right |

TABLE II

CASES TREATED WITH VITAMIN E, SOME INADEQUATELY, WITHOUT SIGNIFICANT CHANGES IN THE INVOLVED PATHWAYS

| Patient | Sex | Age | Duration of Illness | Treatment with alpha toco-pherol | Histologic Picture |
|---------|-----|-----|---------------------------|---|---|
| 7 | М | 53 | 1 yr., 11 mo. | 15 days. | M.S.—A.C., glia and deposition of fat not much different from ordinary cases of amyotrophic lateral sclerosis. |
| 8 | M | 50 | 2½ yrs. | 3 mo., 10 days. | M.S.—moderate destruction. A.C.—moderate destruction. Fa ¹ —come fat droplets but not as much as in usual cases. Holzer—moderate gliosis. |
| 9 | F | 49 | 2 yrs. | 1 yr. — Fairly intensive treat-ment but with interruptions. | M.S.—demyelinization and disintegration of myelin sheaths. Fat—same as average. B'el-chowsky—about same as average case. Holzer—moderate gliosis—slightly less than average. |
| 10 | F | 62 | 2½ yrs. | 7 months with some interruptions. | This case did not differ neuro- pathologically from untreated cases of amyotrophic lateral scle- rosis. |

active deep reflexes but no Babinski or allied signs; diminished abdominals and cremasterics; a motor 5th and supranuclear 7th paresis on the right; paresis of the soft palate; adductor paresis of the right vocal cord; impaired swallowing; paresis of the left trapezius and sternomastoid muscles; fibrillation of the muscles of the tongue and forced laughing and crying.

Laboratory Data: negative.

Course: The patient remained ambulatory and active. He received alpha tocopherol and the other ingredients from February 7, 1940 until September 27, 1940. He developed pneumonia and expired on December 17, 1940.

Autopsy Report – Microscopic examination – The various cortical areas, internal capsule, peduncles and the pyramids in the pons and medulla oblongata disclosed no abnormalities. There were no areas of demyelinization or alteration in the myelin sheaths and axis cylinders

in the pyramidal pathways. The nerve cells of the 10th and 12th nerve nuclei were diminished in number and showed shrinkage, pyknosis, chromatolysis or complete disintegration

Spinal cord: Areas of demyelinization could not be detected with very low power in the myelin sheath preparation (Fig. 1A). With higher magnification, however, there were islands of slight alteration in the size and breaking-down of some of the myelin sheaths in the crossed pyramidal tracts (Fig. 2A). Swelling of a few myelin sheaths could also be detected in parts of the pyramidal tracts that appeared uninvolved (Fig. 2C). In the Bielschowsky preparation, the axis cylinders of the above fibers showed swelling, fragmentation and bulbous terminations within the region of the crossed pyramidal tracts (Fig. 3A). The other axis cylinders within this tract except for swelling did not disclose marked pathological changes. In the Sudan III preparation, fat could hardly be detected in any of the pathways (Fig. 4A). An occasional droplet was seen. In the Holzer preparation, gliosis could not be seen in the pyramidal tracts with lower magnification (Fig. 5A). With higher magnification, however, small perivascular areas of gliosis could be detected (Fig. 6A). In the cresyl violet preparation, there was diminution in the number of anterior horn cells which showed all types of pathological changes such as loss of chromatin, disintegration, shrinkage and slight pyknosis.

Comment: This patient received large doses of Vitamin E and B for a period of seven and one-half months without any noticeable clinical improvement. Histopathologically, there was hardly any demyelinization of the pyramidal tracts and the little that was present was seen only in the spinal cord. Small islands of myelin sheaths and axis cylinders, however, were found destroyed. In the Holzer preparation, there was hardly any gliosis; the little that was present consisted of a few islets of glial fibers. No fatty deposits could be demonstrated in the pyramidal pathways of the spinal cord. This patient also had a supranuclear 5th and 7th which would indicate a lesion of the aberrant pyramidal tract fibers. Degeneration of such fibers could not be demonstrated and it is possible that the Vitamin E may have helped towards the removal of the products of disintegration.

case 2-V.G., a man, aged 60, was admitted to this hospital on April 22, 1940 with a history of twitching of the muscles of the neck, forearms and hands since January 1938. One year later, the patient became

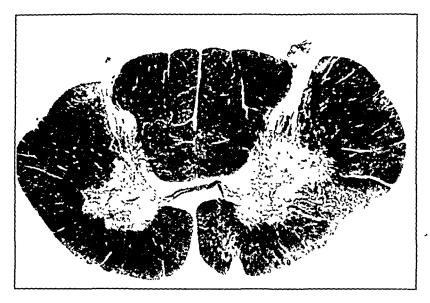


Fig. 1A

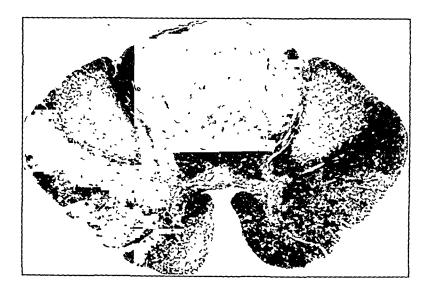


Fig. 1B

Fig. 14 (Case 1)—Lack of visible demyelinization in the pyramidal pathways of a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with Fig. 1B from a non-treated case showing extensive demyelinization of the crossed pyramidal and left direct pyramidal tracts. Myelin sheath stain.

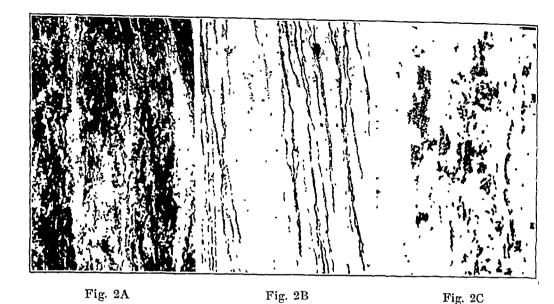
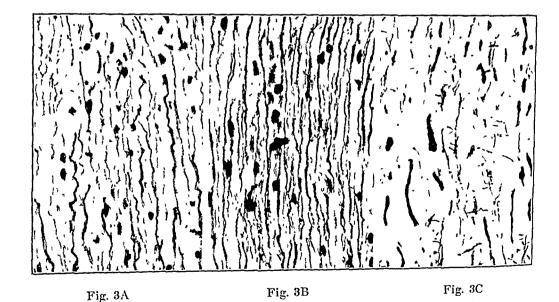


Fig. 2A (Case 1)—Insular myelin sheath destruction from a case treated with Vitamin E. Compare with Fig. 2B of extensive myelin sheath destruction from an untreated case. Myelin sheath x 240. Fig. 2C (Case 1)—Slight disintegration and swelling of single myelin fibers in parts of the pyramidal tracts that appeared uninvolved from a case of amyotrophic lateral sclerosis that received Vitamin E. Myelin sheath x 480.



the (Case 1)—A: Axis cylinders from the crossed pyramidal tract of a case of amyoral sclerosis treated with Vitamin E. Compare with B from a normal case and CASE 2-d case of amyotrophic lateral sclerosis. In A there is slight diminution in and slight tortuosity of axis cylinders when compared with the normal B 22, 1940 Will liseased, fragmented and swollen axis cylinders of the untreated case of arms and handssclerosis in C. Bielschowsky x 480.

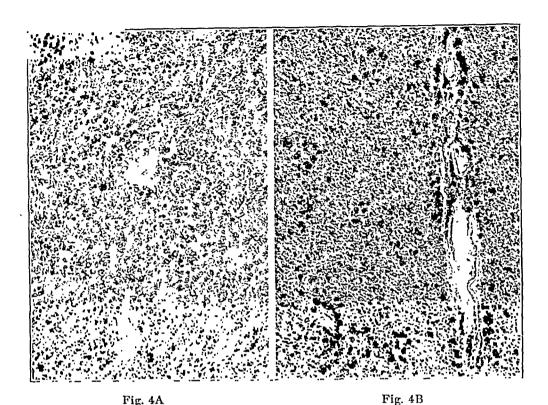


Fig. 4A (Case 1)—Almost complete absence of fat in the pyramidal pathways from a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with Fig. 4B from an untreated case showing lipoid deposits throughout and in the perivascular spaces. Sudan III x 100.

completely chair-ridden and developed hoarseness, choking sensations and fibrillations of the tongue.

Neurological examination disclosed: a shuffling, unsteady gait with bilateral foot-drop; generalized fibrillations and marked atrophy in the intrinsic hand muscles, forearms, thighs and legs; hyperactive deep reflexes with diminished abdominal and cremasteric reflexes but no other pathological reflexes; bulbar speech and atrophy and fibrillation of the tongue.

Laboratory Data: negative except for marked spondylitis of the cervical and dorsal spine.

Course: Shortly after admission the patient received alpha tocopherol and the other ingredients from May 3, 1940 to June 7, 1940. Despite this, there was progression of the symptoms. On May 31, 1940 fibrillations were noted in the muscles of the palate and pharynx. On

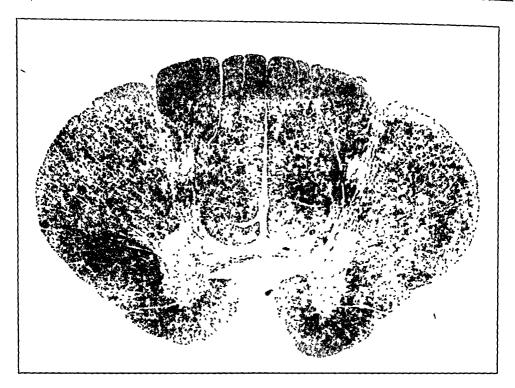


Fig. 7A

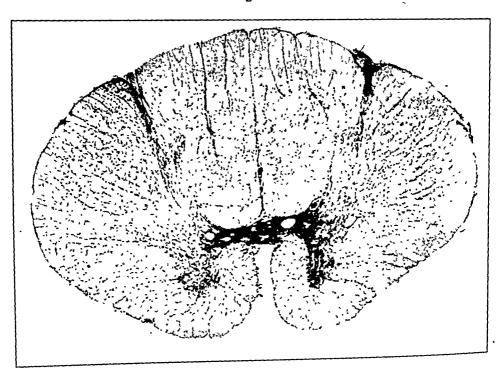


Fig. 7B

Fig. 7A (Case 2)—Notice presence of very slight demyelinization in the pyramidal pathways from a treated case of amyotrophic lateral sclerosis. Myelin sheath stain, Fig. 7B (Case 2)—Absence of dense gliosis in the crossed and direct pyramidal tracts from a case of amyotrophic lateral sclerosis treated with Vitamin E. Holzer stain.

pathways showed slight deposition of fat droplets in the crossed pyramidal tracts. These fatty deposits were less marked than in the untreated cases. In the Holzer preparation, there was only a very slight insular and perivascular gliosis in the crossed pyramidal tracts (Fig. 7B). In the cresyl violet preparation, there was a slight astrocytic proliferation in the involved pathways. The anterior horn cells were decreased in number. diminished in size and showed chromatolytic changes or pyknosis.

Comment: The involved pathways showed less changes in the myelin. axis cylinders and glia than usually seen in untreated cases of amyotrophic lateral sclerosis. The lipoid deposits were also less marked. There was hardly any gliosis and the little that was present was limited to the crossed pyramidal tracts. The illness in this instance only lasted 2 years and 7 months. The bulbar nuclei and the anterior horn cells were severely diseased and apparently uninfluenced by this form of treatment.

CASE 3-R.C., a man, aged 44, was admitted to this hospital on October 18, 1937 with a history of "twitches" in the muscles of the hands, arms and legs since 1934. One year later he was unable to walk unassisted.

Neurological examination disclosed: a spastic gait when supported; marked atrophy and fibrillations of the muscles of the shoulders, arms, hands and lower extremities; loss in muscle power throughout; marked hyperreflexia in the upper and depressed reflexes in the lower extremities; diminished abdominals and absent cremasteric reflexes.

Laboratory Data: negative.

Course: During the first year of his stay in the hospital, there was practically no progression of the symptoms. In November 1939 there developed respiratory difficulties. The patient received alpha tocopherol and the other ingredients from February 7, 1940 until June 12, 1940 when he expired.

Autopsy report—The motor, premotor and parietal cortex, the internal capsule, peduncles and pyramids in the pons appeared normal.

In the *medulla oblongata*, there was a faint pallor of the pyramids. With higher magnification, there was slight disintegration or swelling of single myelin fibers. The nerve cells of the 12th nerve nuclei were diminished in number and chromatolytic. Less severe changes were found in the nerve cells of the nucleus ambiguus.

Spinal cord: There was hardly any pallor in the crossed pyramidal tracts in the myelin sheath preparation. With higher magnification, most of the myelin sheaths in the pyramidal pathways appeared well preserved. A few, insular in distribution, were disintegrated, swollen or showed variability in contour. Occasional swollen sheaths were also found in the apparently unaffected pyramidal tracts. In the Bielschowsky preparation, the axis cylinders in regions of destroyed myelin were broken-down, swollen and occasionally had a corkscrew appearance. Some of the axis cylinders in the unaffected parts of the pyramidal tracts were swollen. In the Sudan III preparation, only a few fat droplets were found in the involved pathways. In the Holzer preparation, the involved pathways showed a very slight perivascular gliosis, insular in distribution. In the cresyl violet preparation, the affected pathways showed a slight astrocytic proliferation. The anterior horn cells especially those in the ventro-lateral and ventro-medial groups were markedly decreased in number. Those present disclosed extensive chromatolytic changes, shrinkage and pyknosis.

Comment: The myelin sheath destruction in the pyramidal and other ventro-lateral tracts and the gliosis was less extensive than in untreated cases of amyotrophic lateral sclerosis. Although the illness lasted six years, the pathological process was less marked than in cases of shorter duration.

CASE 4—R.F., a woman, aged 53, was admitted to this hospital on February 21, 1941 with a history of dysphagia and speech difficulty since December 1939. In March 1941, there appeared paresis of the upper extremities, difficulty in chewing, occasional "twitching" of the hands and left thigh muscles and atrophy of the shoulder muscles.

Neurological examination disclosed: a spastic gait; paresis of the upper extremities; atrophy of shoulder girdle and thenar muscles; fibrillations of neck muscles and left trapezius; total areflexia except for the presence of a slight right KJ; defective right plantar response with a positive Babinski sign on the left and absent abdominals; paresis of the motor 5th; a right supranuclear facial paresis; difficulty in swallowing; slow and nasal speech; limitation in the movement of the tongue with atrophy and fibrillations.

Laboratory Data: essentially negative.

Course: The patient received alpha tocopherol and the other ingredi-

ents. Despite treatment, the patient's illness progressed. She became completely aphonic, developed marked difficulty in swallowing, and expired on June 15, 1941.

Autopsy Report—Only sections of the brain stem and spinal cord were obtained.

Medulla oblongata: There was no demyelinization of the pyramids. With higher power, however, there was an occasional swollen or destroyed myelin sheath. The nerve cells of the ambiguus and 12th nerve nuclei were diminished in number and showed shrinkage, pyknosis, chromatolysis and shadow-like appearance.

Spinal cord: Demyelinization could not be detected with the naked eye. With high power, however, occasional destruction and variation in the size of single myelin fibers could be noted. Some were swollen and fragmented. This process, as in other instances, was insular in distribution. Occasional swelling of a myelin sheath could be detected in regions where the pyramidal tracts appeared intact. In the Bielschow ky preparation, the axis cylinders in the islands of demyelinization showed swelling, knob-like projections and corkscrew processes. In other regions of the pyramidal tracts, occasional swelling of the axis cylinders were also noted. In the Sudan III preparation, there were hardly any fat droplets in the involved pathways. In the Holzer preparation, gliosis could not be detected with the naked eye. In the slight areas of myelin sheath destruction, however, there was a faint, patchy, insular, perivascular gliosis.

Comment: This patient received Vitamin E therapy for a period of about seven and one-half months without any improvement in the neurological picture. The histopathological process of the myelin sheaths, axis cylinders, and glia in the spinal tracts showed a distinct difference when compared with those in the untreated cases.

CASE 5—H.F., a woman, aged 70, was admitted on February 3, 1941 with a history of progressive weakness of the extremities since September 1939. In November 1939 there developed dysphagia, regurgitation of food through the nose and excessive salivation.

Neurological examination disclosed: weakness, atrophy and fibrillations of the muscles of the upper extremities and sternocleidomastoids; hyperactive reflexes with bilateral Hoffman and defective plantar response; palatal paresis; defective gag reflexes and dysphagia; marked dysarthria, sialorrhea, atrophy and fibrillations of the muscles of the tongue.

Laboratory Data: negative.

Course: Patient received alpha tocopherol and the other ingredients from February 5, 1940 until April 14, 1940. The condition remained unaffected by the therapy and the bulbar signs progressed. The patient expired on October 8, 1940.

Autopsy Report: Only the brain stem and spinal cord were removed. Pons: There was a faint pallor of the pyramids. With high power, occasional swelling, slight disintegration and variation in size were noted in a few fibers.

Medulla oblongata: There was a slight demyelinization of both pyramids with changes similar to those seen in the pons. In the cresyl violet preparation, the nerve cells of the ambiguus and 12th nerve nuclei were diminished in number and showed chromatolysis, vacuolization and shrinkage.

Spinal cord: There was slight demyelinization of both crossed pyramidal tracts best noted in the cervical regions and much less in the lumbosacral region. With high power, small islands of fibers in the crossed pyramidal pathways disclosed disappearance of myelin, swelling, disintegration and variations in size. Occasional swelling of a single myelin fiber was noted in apparently unaffected parts of the pyramidal tracts. In the Bielschowsky preparation, a few of the axis cylinders, especially in the islands of myelin sheath destruction, were swollen, broken-down and had a corkscrew appearance. In the Sudan III preparation, there were only a few fat granules in one region of the right crossed pyramidal tract. In the Holzer preparation, gliosis could not be seen with the naked eye; with higher magnification, a few islands of slight perivascular gliosis were noted in the involved regions. In the cresyl violet preparation, the anterior horn cells were diminished in number and showed loss in chromatin, pyknosis and sclerosis or severe cell changes.

Comment: This patient was treated with large doses of Vitamin E without clinical improvement. Histopathologically, demyelinization and destruction of axis cylinders and gliosis were slight.

case 6—T.R., a man, aged 54, was admitted to this hospital on July 2, 1940 with a history of increased salivation, difficulty in manipulating the tongue and in pronouncing the letter "L" and dragging of the left foot since February 1939. Later he experienced "jumping" sensation in the trunk and in the upper and lower extremities. In March 1940 speech became unintelligible and he could no longer move his tongue from

side to side or protrude it beyond the teeth.

Neurological examination disclosed: a spastic gait; weakeness of extremities with atrophy and fibrillations, especially in the muscles of the thenar and hypothenar eminences; generalized hyperreflexia with bilateral Hoffman, patellar and ankle clonus; complete palatal paresis; a speech limited to grunts; atrophy and fibrillations of the tongue muscles.

Laboratory Data: negative.

Course: The patient received alpha tocopherol and the other ingredients from August 2, 1940 until September 12, 1940. He was unable to swallow and had to be fed through a nasal catheter. After Vitamin E therapy, he was able to swallow a little but this function failed again. Finally the patient became bed-ridden and expired on February 4, 1941.

Autopsy Report: Only the spinal cord was obtained. In the myelin sheath preparation, there was a slight demyelinization of the right and very slight pallor of the left crossed pyramidal tracts (Fig. 8A). The myelin sheaths of this pathway were partially destroyed, especially on the right. Occasional swelling of myelin sheaths were noted in parts of the unaffected pyramidal tract. In the Bielschowsky preparation, the corresponding axis cylinders on the right were broken-down, swollen, had knob-like projections and a corkscrew appearance. On the left side, moderate axis cylinder destruction was present only in the small islands of myelin sheath degeneration. In the Sudan III preparation, fatty accumulations were present in both pyramidal tracts; a few fat droplets were present in the direct pyramidal, Holweg and ventro-spino-thalamic tracts. In the Holzer preparation, there was a dense gliosis in the right crossed pyramidal (Fig. 8B) and left lateral spino-thalamic tracts, and a slight gliosis in the left crossed pyramidal tract (Fig. 8B). In the right crossed pyramidal tract, astrocytic proliferation was more marked than on the left. This was best noted where there was severe myelin sheath destruction. The anterior horn cells were diminished in number, shrunken and showed loss in chromatin, shadow-like appearance or complete disintegration.

Comment: The pathological process in this instance was more extensive on the right side of the cord, as evidenced by the myelin sheath and axis cylinder destruction, the heavy deposits of lipoid and the extensive gliotic process. In the other half of the cord, the pathological process was very slight and almost identical with the process in the cases with little cord involvement.

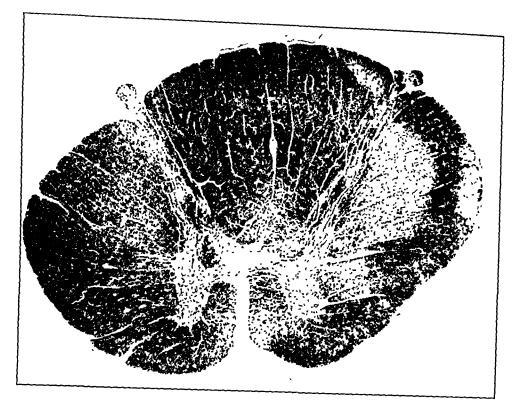


Fig. 8A

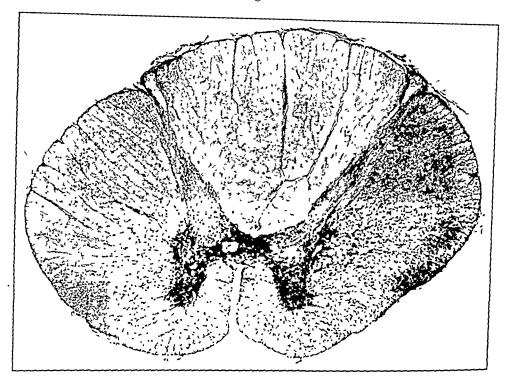


Fig. 8B

Fig. 8A (Case 6)—Transverse section showing slight pallor of the left and demyelinization in the right crossed pyramidal tracts. Myelin sheath stain.

Fig. 8B (Case 6)—Gliosis present only in the right crossed pyramidal tract but absence of gliosis in the left, except for the left lateral spinothalamic tract. Holzer stain.

II—CASES TREATED WITH VITAMIN E, SOME INADEQUATELY, WITHOUT SIGNIFICANT CHANGES IN THE INVOLVED PATHWAYS.

CASE 7—F.J., a man, aged 53, was admitted to this hospital on December 25, 1938 with a history of weakness of the legs since March 1938. This progressed and the patient finally was unable to walk without the use of a cane. In August 1938 he experienced spasms of the muscles of the thighs, and shortness of breath when speaking.

Neurological examination disclosed: a spastic gait when assisted in walking; marked fibrillations and atrophies of the muscles of the lower extremities, shoulders, abdomen and back; weakness in the extensor muscles of the legs; hyperactive tendon reflexes throughout, defective plantar responses and absent abdominal reflexes.

Laboratory Data: negative.

Course: There was a gradual progression of symptoms with extension of the process to the upper extremities, tongue, pharynx and larynx. This patient did not receive intramuscular injections of alpha tocopherol but received from February 5, 1940 to February 20, 1940 two tablets of ephynal by mouth daily and 5 mgm. thiamin chloride without any improvement in the neurological signs. He expired on February 23, 1940.

Autopsy Report—The cortex, internal capsule and peduncles showed no abnormality. Extensive demyelinization of the pyramids with destruction of myelin and axis cylinders began in the medulla oblongata. The nerve cells of the nucleus ambiguus and of the 12th nerve nucleus were diminished in number, showed marked loss in chromatin or were sclerotic.

In the spinal cord, there was extensive demyelinization of the crossed pyramidal tracts with slight involvement of the direct pyramidal and other ventro-lateral tracts (Fig. 9A). The myelin sheaths and axis cylinders in the pyramidal tracts showed the usual destructive changes seen in amyotrophic lateral sclerosis. In the Sudan III preparation, these pathways were heavily loaded with fat granules. Single fat droplets were also scattered throughout the ventro-lateral tracts. In the Holzer preparation, there was a dense gliosis in the region of the crossed pyramidal tracts (Fig. 9B). In the cresyl violet preparation, there was a marked astrocytic proliferation in the involved pathways. The anterior horn cells were markedly diminished in number especially the ventro-medial



Fig. 9A

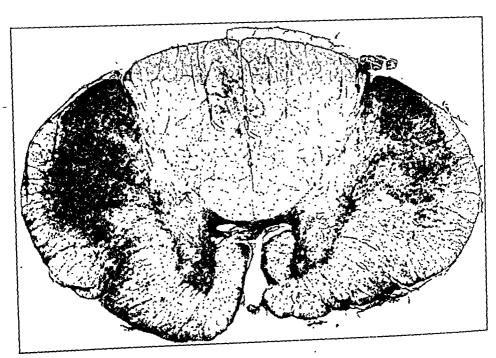


Fig. 9B

Fig. 9A (Case 7)—Demyelinization of crossed pyramidal tracts from a case of amyotrophic lateral sclerosis inadequately treated with Vitamin E. Compare with adequately treated cases—Figs. 1A and 7A. Myelin sheath stain.

Fig. 9B (Case 7)—Gliosis in region of crossed pyramidal tracts from the same case. Compare with adequately treated cases—Figs. 5A and 7B. Holzer stain.

and ventro-lateral groups. Those which persisted were shrunken and showed marked loss in chromatin and their processes.

Comment: This patient who received ephynal orally for only a period of 15 days did not show any clinical improvement. The histopathological picture did not differ much from the average untreated case of amyotrophic lateral sclerosis.

CASE 8—B.J., a man, aged 50, was admitted to this hospital on July 19, 1939 with a history of inability to pronounce words clearly since December 1938. This condition progressed so that he could barely be understood. In March 1939 there developed weakness in the right lower extremity and dysphagia.

Neurological examination disclosed: a slow, broad-based unsteady gait with dragging of the right foot; fibrillary twitchings of the muscles of the shoulders and neck; atrophy of the muscles of right shoulder, thenar eminences, and calf; difficulty in performing skilled acts; hyperactive deep reflexes with bilateral Hoffman, Rossolimo and Babinski signs; dysarthric and nasal speech and fibrillations and atrophy of the muscles of the tongue.

Laboratory Data: negative.

Course: For seven months prior to admission to this hospital, the patient received brewer's yeast tablets. At Montefiore the patient received orally from February 7, 1940 to May 10, 1940 two tablets of ephynal daily, 5 mgm. of thiamin chloride, 4 cc. of wheat germ oil, bile salts and cod liver oil with continued progression of symptoms: He developed pneumonia and died on May 13, 1940.

Autopsy Report: Only the brain stem and the spinal cord were obtained.

Medulla oblongata: In the myelin sheath preparation, there was a slight bilateral demyelinization of both pyramids, definitely less extensive than in untreated cases of amyotrophic lateral sclerosis. Disintegration of myelin sheaths and axis cylinders could be observed with high magnifications. The nerve cells of the 10th, 11th and 12th nerve nuclei were diminished in number and showed severe cell changes of Nissl, chromatolysis, disappearance of the Nissl substance, displacement of nuclei at the periphery and pyknosis.

Spinal cord: There was moderate demyelinization of the crossed pyramidal tracts with sparing of the direct. With higher power, there was swelling and some destruction of the myelin sheaths and axis cylin-

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ders but not as much as in the ordinary cases of amyotrophic lateral sclerosis. In the Sudan III and Marchi preparations, the involved pyramidal tracts contained fatty deposits but not in the excessive amount seen in the untreated case of amyotrophic lateral sclerosis. In the Holzer preparation, there was a moderate gliosis in the crossed pyramidal tracts which was not as extensive as in the ordinary case of amyotrophic lateral sclerosis. In the cresyl violet preparation, the involved pathways contained proliferating astrocytes. The anterior horn cells were diminished in number; some were shrunken and pyknotic, others showed chromatolytic changes or were completely disintegrated.

Comment: This patient received Vitamin E orally for 3 months without any clinical effects. Histopathologically, however, the involved pathways did not show the extensive changes seen in the average untreated case of amyotrophic lateral sclerosis. This was especially true of the demyelinization and gliotic process. The diseased anterior horn cells were unaffected by the therapy.

CASE 9—K.A., a woman, aged 49, was admitted to this hospital on July 27, 1939 with a history of generalized weakness, fatigue, difficulty in speech, swallowing, chewing and choking episodes and nasal regurgitation since November 1938. Later she experienced "twitchings" of the muscles of the neck and anterior part of the chest.

Neurological examination disclosed: a slightly spastic gait; weakness of the deltoid and scapular muscles, right more than the left; atrophy of the shoulder muscles with fibrillation, hyperactive deep reflexes in the uppers with Hoffman signs and hypoactive reflexes in the lower extremities without pathological reflexes; hyperactive jaw jerks; bilateral weakness of the 5th, 7th, 9th and 12th cranial nerves; marked dysarthria and dysphagia, and marked atrophy and fibrillations of the tongue muscles.

Laboratory Data: negative.

Course: The patient received intramuscular injections of alpha tocopherol and the other ingredients from September 29, 1939 until September 24, 1940 with frequent interruptions. There was a gradual relentless progression of the symptoms with increasing weakness and frequency of dyspneic episodes and sialorrhea. She became stuporous and expired on November 26, 1940.

Autopsy Report-Only the medulla oblongata, pons and spinal cord

were removed.

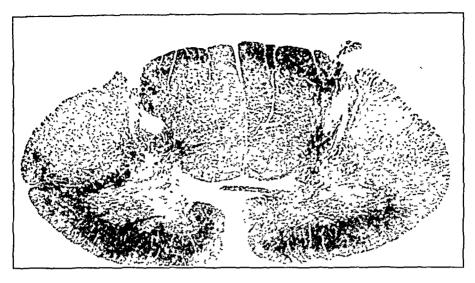


Fig. 10

Fig. 10 (Case 9)—Case of amyotrophic lateral sclerosis treated intensively with Vitamin E for 1 year, but with interruptions, showing demyelinization of the crossed pyramidal tracts. Myelin sheath stain.

Medulla oblongata: Both pyramids were demyelinated and contained honeycombed areas. The myelin sheaths showed various pathological changes such as disintegration, swelling and variations in size. In the cresyl violet preparation, the nerve cells of the 10th and 12th nerve nuclei were diminished in number and showed pathological changes such as chromatolysis, peripherally displaced nuclei, shrinkage or shadow-like appearance.

Spinal cord: Demyelinization was limited to the crossed pyramidal and slightly to the left direct pyramidal tract (Fig. 10). With high power, the crossed pyramidal tracts had a slight honeycombed appearance. There was destruction, swelling and variations in the size of the myelin sheaths. The axis cylinders of the involved pathways were either destroyed, thin, swollen or had corkscrew processes and bulbar terminations. In the Sudan III preparation, the involved pathways contained an abundance of fat globules; some were collected in the perivascular spaces. In the Holzer preparation, the crossed pyramidal tracts showed dense gliosis as seen in the average case of amyotrophic lateral sclerosis. Slight gliosis was also found in the left direct pyramidal tract.

In the cresyl violet preparation, the anterior horn cells especially the ventro-medial and ventro-lateral groups were extensively diminished in number; they showed chromatolytic changes, granular disintegration, shrinkage, pyknosis and occasional corkscrew processes.

Comment: This patient received intensive Vitamin E orally and parenterally without improvement for a period of one year. In contrast with some of the other cases that received Vitamin E, the pathological process in the pyramidal tracts did not differ from cases of amyotrophic lateral sclerosis that did not receive such therapy.

CASE 10—M.R., a woman, aged 62, was admitted to this hospital on September 13, 1939 with a history of weakness of the left hand and "twitchings" in the muscles since January 1939. This condition progressed and spread to both upper and lower extremities.

Neurological examination disclosed: a spastic gait; weakness of hands, forearms, and lower extremities; atrophy of hand and forearm muscles; fibrillations of thigh and shoulder muscles; generalized hyperreflexia with bilateral Hoffman and ankle clonus; absent abdominal reflexes and fibrillations of the tongue.

Laboratory Data: negative.

Course: The patient received alpha tocopherol intramuscularly and the other ingredients from February 24, 1940 until September 24, 1940 with interruptions. During this period, the patient developed difficulty in talking and swallowing. In addition to the previous findings, there was a bilateral Babinski. On June 5, 1941 she suddenly collapsed, became cyanotic and died in respiratory failure.

Autopsy Report: In the premotor and motor regions, a number of the pyramidal cells had a shadow-like appearance. The giant pyramidal cells of Betz were diminished in number and showed pathological changes such as slight shrinkage and absence of Nissl substance. The internal capsule and peduncles did not show areas of demyelinization with low power, but with higher power, rarefaction and destruction of myelin fibers were noted. In the Sudan III preparation, these pathways contained fat droplets.

In the pons, there was pallor of the pyramids and the myelin sheaths

were fragmented, swollen and varied in size.

Medulla oblongata: At this level, both pyramids were completely demyelinated and severe changes were found in the myelin sheaths and

axis cylinders. In the cresyl violet preparation, the nerve cells of the 12th nerve nucleus were diminished in number, shrunken and showed pigment atrophy and severe chromatolysis. Similar changes were found in the nucleus ambiguus.

Spinal cord: There was extensive demyelinization of the crossed and direct pyramidal tracts throughout all segments. The cord had a honeycombed appearance and the myelin sheaths were severely destroyed. In the Bielschowsky preparation, the axis cylinders, although they showed swelling and bulbous terminations, were not as severely damaged as the myelin sheaths. Here and there, completely destroyed axis cylinders could be noted; some had a corkscrew appearance. In the Sudan III preparation, the involved pathways contained fatty deposits but not as much as in the untreated cases. In the Holzer preparation, there was a dense gliosis of the crossed pyramidal tract and slight in the region of the direct pyramidal tracts.

Comment: In this case, there was implication of the motor cortex and severe involvement of the pyramidal tracts extending from the internal capsule to the spinal cord. Although this patient received Vitamin E for a period of about seven months, the changes in the affected pathways were not much different from the untreated cases of amyotrophic lateral sclerosis.

ANALYSIS OF MATERIAL

Clinical Evaluation: These cases present a few clinical facts worth discussing. There were six males and four females, a distribution which conforms with observations that the incidence of amyotrophe lateral sclerosis is greater in males than females. The ages of these patients were: two in the fifth decade, four in the sixth, three in the seventh, and one in the eighth. The duration of the illness in most instances was between two and two and one-half years except Case 3 who lived six years after the onset of the illness and Cases 1, 4 and 5 who lived twenty, eighteen and thirteen months respectively.

The first six treated cases that showed a different histopathologic picture from the usual picture in non-treated cases disclosed severe atrophy and fibrillations of the muscles especially in the distal parts of the extremities, more so in the upper than in the lower. The pyramidal tract signs consisted of a generalized hyperreflexia in all, diminished or absent abdominal reflexes in Cases 1, 2, 3, 5 and 6, Hoffman in Cases

5 and 6, Babinski or allied signs only in Case 4. These cases ought not to be confused with progressive spinal muscular atrophy, a disease of anterior horn cells without pyramidal tract lesions, where there is widespread atrophy of muscles and absent or markedly diminished deep reflexes. Furthermore, the onset of the illness in progressive spinal muscular atrophy starts at a much earlier age and lasts much longer than in amyotrophic lateral sclerosis, at times from ten to twenty years. Kinnier-Wilson¹¹ and others recognize that atrophy of muscles in amyotrophic lateral sclerosis may become so extreme as to abolish or decrease the respective reflexes. "There is as it were a conflict between the respective tone-increasing and tone-reducing influences of supranuclear and nuclear lesions" (Kinnier-Wilson¹¹). In an analysis of thirty-six other cases of this illness that came to necropsy, fifteen with severe demyelinization of the pyramidal tracts, because of the marked atrophies, disclosed diminished or absent reflexes. It should also be emphasized that most of the cases in this presentation as in the normal cases of amyotrophic lateral sclerosis died because of involvement of the bulbar nuclei, a process which rarely occurs in progressive spinal muscular atrophy.

Kinnier-Wilson who is inclined to place progressive spinal muscular atrophy and amyotrophe lateral sclerosis in the same group states "difficult as it is to reach a firm conclusion, the lesions of the Charcot type (amyotrophic lateral sclerosis) are so characteristic, and when advanced, so different from those of nuclear amyotrophy (progressive spinal muscular atrophy), that in my opinion the fact outweighs other considerations; they comprise much more than the mere addition of upper to lower motor neuronic disease. While I consider this divergence more striking than the similarities, the occurrence of gradations from one to the other, and also in the direction of "subacute anterior poliomyelitis" must be admitted; not all of either kind run true to type. For descriptive purposes [underscored by Davison], however, it is best to take the two varieties together, inclusive of intermediate and aberrant clinical forms."

Of the ten cases, two (7 and 8) received ephynal by mouth; the others also received alpha tocopherol intramuscularly. Case 7 received the treatment only for a period of 15 days. The others were treated from five weeks to seven and one-half months. Cases 9 and 10 were treated for one year and seven months respectively but with interruptions. As will be seen this may have had some relationship to the histopathologic changes. None of these cases except Case 6 showed any

improvement in the neurological symptoms.

Histopathologic Evaluation: Nerve cell changes: The histopathological changes in the involved nerve cells of the medulla oblongata (usually 10th and 12th nuclei) and anterior horn cells in the spinal cord were the same in the treated as in the untreated cases of amyotrophic lateral sclerosis. This was true both in regards to the number and character of the nerve cell changes. The involvement of the bulbar nuclei and the progress of the changes in these nerve cells resulted in death in most of these cases.

Pathway changes: On the other hand, definite changes were present in the myelin sheaths, axis cylinders, fat and glia.

In Cases 1, 2, 3, 4, 5 and 6, or 60 per cent of the cases, the pathological process in the involved pathways of the central nervous system especially of the spinal cord differed entirely from the untreated cases. In these, except Case 6, demyelinization of the crossed pyramidal tracts in the myelin sheath preparation could hardly be detected with the naked eye (Fig. 1A). This was not true in the untreated cases where the demyelinization stands out prominently (Fig. 1B).

Occasionally a case of amyotrophic lateral sclerosis may show little demyelination in the pyramidal pathways. Two such cases were found among the other thirty-six cases that came to necropsy. One of these turned out to be a case of spastic pseudosclerosis. The diminution of demyelinization in the first six consecutive cases that were treated certainly could not be a mere coincidence. Furthermore, even the other four less adequately treated cases showed changes which were slightly less severe than in the ordinary run of amyotrophic lateral sclerosis.

With higher magnification, the involved myelin sheaths, usually grouped in small islands, were fragmented or swollen (Fig. 2A). When compared with myelin sheath changes in untreated cases, it can be definitely stated that this process was not 1/10th as extensive as in the average case of amyotrophic lateral sclerosis (Fig. 2B). Occasional swelling of myelin sheaths could also be detected in parts of the pyramidal tracts which did not appear demyelinated (Fig. 2C). In Case 6, the right pyramidal tract was demyelinated and destruction of myelin sheaths in this pathway was more extensive (Fig. 8A).

The pathological process in the axis cylinders except those of the right pyramidal tract in Case 6 was essentially limited to the islands of involved myelin sheaths. Here the changes, although much less intense

than in the untreated cases, consisted of swelling, slight fragmentation, bulbous terminations, and corkscrew appearance (Fig. 3A). Various degrees of swelling of the axis cylinders were also noted in parts of the pyramidal tracts which did not appear demyelinated.

In the Sudan III preparation, the amount of fatty deposits differed in these six treated cases. There were hardly any fatty deposits in the lateral or anterior pyramidal tracts in Cases 1 and 5 (Fig. 4A). Cases 2, 3 and 4 had less fat than the untreated cases, while in Case 6, the fatty contents did not differ much from the untreated cases.

Most of the outstanding changes, however, were noted in the glia tissue. In the untreated cases of amyotrophic lateral sclerosis, there was a dense gliosis in the involved pathways easily detected with the naked eye in the Holzer preparation (Fig. 5B). In these six treated cases, except for the right pyramidal tract in Case 6 (Fig. 8B), the gliosis could hardly be observed with the naked eye (Fig. 5A). With higher magnification, however, small perivascular islands of gliosis (Fig. 6A) were noted in the region of the involved myelin sheaths and axis cylinders.

In the seventh case, which was treated for only a short period of time (15 days) with ephynal by mouth, the myelin sheaths axis cylinders, fat content and glia reaction did not differ from the untreated cases of amyotrophic lateral sclerosis. In cases 8, 9 and 10, the destruction of myelin sheaths, axis cylinders and the gliosis were not much different, although slightly less than in the untreated cases. In Case 8 the fatty accumulations in the affected pathways were definitely less than in the untreated case. The gliotic process in these cases was moderate in degree and slightly less intense than in the ordinary cases. In order to be on the conservative side, the changes in these cases were considered about the same as those found in untreated cases.

Certain factors may have played a role in the histopathological changes of these three cases. In Case 8 the patient received ephynal orally, but did not receive alpha tocopherol intramuscularly. Cases 9 and 10 were treated for one year and seven months respectively including intramuscular injections of alpha tocopherol, but the treatment was interrupted several times. This may have influenced the lack of improvement in the involved pathways. The age, the duration of the illness and the time the treatment was begun in these instances did not differ from the other treated cases.

Factors influencing the changes in the affected pathways: As was previously demonstrated (Davison¹²) in untreated cases of amyotrophic lateral sclerosis, the diseased process affects the upper and lower motor neurons. The upper motor neuron can be involved, either at its point of origin in the giant pyramidal cells of Betz or anywhere along its course. The upper motor neuron lesion is most pronounced in the spinal cord and is characterized by destruction of the myelin sheaths and axis cylinders and a dense glial scar. Once the myelin sheaths and axis cylinders in the involved pathways are completely destroyed, their regeneration is problematic. Some observers are under the impression that regeneration of axons in involved pathways of the spinal cord may take place under favorable conditions in a manner similar to regeneration of axons in peripheral nerves. By the new methods of neurofibrillar study, it has been demonstrated that the production of new fibers, clubs, cones and ramified axons may occur in various lesions of man and animals. These findings, while they demonstrate signs of repair comparable in principle with those of the central stump of the peripheral nerve, do not contradict the conception of the impossibility of complete regeneration of axis cylinders in the spinal cord. These later investigations have also demonstrated that after a certain length of time the restoration of the axon in the spinal cord stops, that the axon atrophies and that finally the nerve sprouts break down completely.

On the basis of the above investigations, it can hardly be expected that completely destroyed myelin sheaths and axis cylinders in the spinal cord should regenerate. In the six out of the ten cases of amyotrophic lateral sclerosis adequately treated with Vitamin E there was no question that the involved myelin sheaths and axis cylinders were less affected when compared with similar preparations of untreated cases. When I11 observed similar improvement in the cases of subacute combined degeneration adequately treated with liver, I then postulated that axis cylinders may undergo a reversible reaction provided they are not severely affected and if the patient receives early and adequate treatment. Can this explanation also be applied to amyotrophic lateral sclerosis? This cannot be answered as easily as in subacute combined degeneration. There is a possibility in amyotrophic lateral sclerosis, as in subacute combined degeneration, of a reversibility of the reaction if the axis cylinders are not severely destroyed. In other words, damaged but not completely destroyed axis cylinders, under favorable circumstances, may regenerate or be restored nearly to their normal state. This is the only possible explanation that can be offered from the above observations. Under these circumstances, clinical improvement in the neurological signs and symptoms in the above cases should have been expected. This, as already stated, did not occur. How can this discrepancy be explained? The possibility that these patients did not receive adequate quantities of Vitamin E and/or were not treated sufficiently early must be considered. In some instances of amyotrophic lateral sclerosis, besides the lack of Vitamin E which may cause the disease, there is the possibility as suggested by Wechsler,1 of another unknown factor, which may play a role in the absorption of the vitamin. These are questions which so far have not been settled and cannot be answered with certainty. It is possible that in some instances, early and adequate administration of Vitamin E may arrest the process in the involved myelin sheaths and axis cylinders and may restore their function provided they are not completely damaged.

The lessened or almost complete disappearance of fatty deposits in the treated cases can be explained on the basis that the Vitamin E treatment may have resulted in a decline or cessation of the pathologic process, thus helping towards the removal of the products of disintegration.

The absence of intense gliosis or the regression of the gliosis in the treated cases appears disturbing for the contrary would be expected in areas of myelin sheath and axis cylinder repair. In a number of cases of subacute combined degeneration that received adequate liver therapy studied by the author, 13 the improvement noted in the affected pathways was accompaniel by a dense gliosis. There is a remote possibility that the restoration or reversion to a normal or nearly normal glia reaction as seen in the treated cases of amyotrophic lateral sclerosis is parallel to the observed restoration of the myelin sheaths and axis cylinders. If this should be true, then it may be postulated that the reversibility of reaction took place all along the line, affecting simultaneously and equally or nearly equally the damaged myelin sheaths, axis cylinders and glial tissue.

One other disturbing factor in this study were the changes in the nerve cells in the involved bulbar nuclei and anterior horns which did not differ in the treated from the untreated cases. Clinically, however, Wechsler¹ observed that the fibrillations and the bulbar signs especially the recent ones cleared up, whereas, the pseudobulbar symptoms re-

sponded less well or not at all.

There are still many questions regarding the treatment of amyotrophic lateral sclerosis which will have to be answered. While the efficacy of Vitamin E therapy in this disease is still problematic, the above histopathologic findings and the clinical (Wechsler¹) evidence indicate that this form of treatment should be continued experimentally.

SUMMARY AND CONCLUSIONS

Ten cases of amyotrophic lateral sclerosis were treated with Vitamin E and alpha tocopherol and except for one, none responded clinically to this form of treatment.

Histopathologically, however, in six of the intensively treated cases the destruction of the myelin sheaths and axis cylinders was found to be much less intense than in the untreated cases. The dense gliosis which is usually present in amyotrophic lateral selerosis was diminished or almost absent in those that received Vitamin E. The lessened myelin sheath and axis cylinder destruction and the faint gliosis in these instances were perivascular and insular in distribution. In one of these (Case 6), the lessened changes were limited to one side of the cord only. The nerve cells of the involved bulbar nuclei and anterior horns remained unchanged and showed no signs of reversibility. The ultimate cause of death was bulbar in nature.

The histopathologic processes in the other 4 less intensively treated cases, although less extensive, were considered about the same as those found in untreated cases.

There is a possibility that Vitamin E therapy resulted in a reversal of the reaction of degeneration affecting simultaneously and nearly equally the damaged myelin sheaths, axis cylinders and glia in amyotrophic lateral sclerosis.

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TREATMENT OF PROSTATIC CARCINOMA*

BENTAMIN S. BARRINGER

(Huggins). What the future holds we do not know. The treatment so ably developed by Dr. Huggins may eventually lead to complete understanding and cure of this lethal disease.

The dramatic improvement following orchidectomy in some patients with prostatic cancer gives me the same thrill that I experienced when twenty-five years ago I saw the first metastasis from a teratoma testis disappear under the radium pack and the first bladder cancer, to which radium was applied, vanish.

Because orchidectomy with any added hormone medication is far from being one hundred per cent successful it is possible that some combination of orchidectomy and the past not wholly ineffective treatments should be used.

Allow me to review very briefly the pre-orchidectomy period.

Radiation treatment by means of radon-bearing needles or radon seeds has afforded control in twenty-one of 352 cases (6 per cent) for periods of between five and nineteen years. These patients are, so far as can be seen, free of cancer. Radiation treatment has been of value in maintaining the patency of the urethra and so enabling a patient to empty his bladder during the years he has to live. Deep x-ray therapy has been of little use in controlling the disease.

Radical removal of the small prostatic cancer has likewise effected a cure in a small percentage of prostatic cancers. This operation, devised and elaborated by Young, has been done by many urologists-Smith, Hinman and others for many years.

Read December 3, 1942 at the Stated Meeting of The New York Academy of Medicine in association with the Section of Genito-Urinary Surgery.

So is summarized in half a page the results of a prodigious amount of work covering twenty-five years.

In the pre-orchidectomy period there were four developments all of which have carried over to and been extremely valuable in the orchidectomy period. These are:

- 1. Aspiration biopsy.
- 2. Transurethral resection.
- 3. Recognition that prostatic carcinoma often metastasizes to bone.
- 4. Acid and alkaline serum phosphatase determination.

Aspiration biopsy of the prostate was developed at the Memorial Hospital and after using a series of different puncturing instruments a simple long spinal type aspirating needle was found best. It was found that such a needle could be introduced through the perineum into the prostate with a guiding finger in the rectum and by means of suction a plug of prostatic tissue large enough for staining could be obtained. In this way early and puzzling cases could be accurately diagnosed. The method is about 70 per cent successful. The type of carcinoma cannot, however, be determined in the specimen.

Transurethral resection has had wide use and is of much value in coping with that most troublesome symptom of prostatic cancer, urinary retention. Two things are accomplished by it: first, relief of retention; second, a pathological specimen is obtained for accurate diagnosis. In the hands of some urologists it has been done multiple times during the period which the patient lived with ever-recurring retention.

Over the course of the years it has been found and noted in many instances that prostatic carcinoma very often metastasizes to bone. These metastases generally are osteoplastic and therefore cast a dense shadow on the x-ray film. Whether these metastases be venous or lymphatic, they occur most often in the lumbar spine and pelvis.

The determination and meaning of the acid and alkaline serum phosphatase date back to 1935 when Kutscher and Wolberg¹ reported that there was acid phosphatase in the prostate.

Gutman, Sproul, and Gutman² in 1936 reported both acid and alkaline phosphatase in bones which were the site of prostatic cancer metastases. Two weeks after this publication Woodard (unpublished) found excess acid phosphatase in the serum of a patient with metastatic carcinoma of the prostate. The Gutmans published three papers,^{3,4,5} two in 1938 and one in 1939 discussing the elevation of acid phosphatase in

the serum of patients with metastasizing carcinoma of the prostate.

Barringer and Woodard⁶ published in 1939 a paper, read before the American Association of Genito-Urinary Surgeons in May 1938, giving findings in a number of cases of prostatic carcinoma and suggested that: "There is apparently a direct relation between the laying-down of bone in prostatic carcinoma and the blood phosphatase. The determination of the blood phosphatase may have some value in diagnosing osteoplastic metastases, possibly before such metastases are revealed by radiograph. It unquestionably is of value in the differential diagnosis of the source of a bone metastasis."

In 1941 Woodard and Higinbotham⁷ discussed the changes in the acid and alkaline phosphatase of patients with prostatic cancer following roentgen therapy.

The Gutmans' last papers on the "Theory and application of the serum 'acid' phosphatase determination in metastasizing prostatic carcinoma" was published in October 1942.

Suffice it to say here that serum "acid" phosphatase is generally elevated if the prostatic carcinoma is of any size and the serum alkaline phosphatase is elevated if there are bone metastases. Therefore, we have a method of diagnosis and differential diagnosis of the prostatic carcinoma itself and of the bone metastases; we also have a method of estimating recessive changes in both of these.

The orchidectomy period has demonstrated that simple orchidectomy may in some cases cause complete recession of both the prostatic carcinoma and the bone metastases. This, of course, is revolutionary. The probable rationale is that the testicular hormone is necessary for prostatic activity. Remove the testis and one inactivates the prostate and also the prostatic carcinoma. Because metastases are controlled it is assumed that they possess metabolic attributes in some manner similar to those of the prostate. Suggestive evidence of this is that both prostate carcinoma and prostatic metastases contain "acid" phosphatase.

We know that some cancers are capable of performing the same functions as the normal tissues from which they arise. An example of this is the classic case of von Eiselberg quoted by Ewing,⁹ in which myxedema followed total extirpation of the thyroid for cancerous goitre; but disappeared on the development of a metastatic focus.

That there must be other extra-testicular elements controlling both the prostatic carcinoma and the metastasis is evident because Huggins reports regression in but 50 per cent of cases and we in considerably less. Assays of the urine of castrated patients show this. That is, in urine there are excreted 17-ketosteroids (androgen) and also estrogens. When the testicles are removed, the 17-ketosteroids, instead of decreasing, remain constant or may rise. This indicates that there is some other source of the 17-ketosteroids. We know that the adrenals are at least one other source of androgens.

Orchidectomy and Bone Metastases. We have had fifty cases in which orchidectomy has been performed. Because of various factors, in but twenty-eight of these cases are the records sufficiently complete to report. That is, in these twenty-eight cases the pathological examination is complete; pre- and many post-orchidectomy phosphatase examinations have been made and pre- and post-orchidectomy roentgenograms made, and the patients have survived a sufficient length of time after orchidectomy to enable some conclusions to be drawn.

Of these twenty-eight cases, seventeen had high alkaline phosphatase (indicating bone metastases) and nineteen had bone metastases shown by roentgenogram. In five of nineteen cases the bone metastases worsened, but in size and number. In one there was no change. In one there was extension of bone metastases in some areas and in others the metastases grew less dense. In two cases with atypical (osteolytic) bone metastases there was some healing, five and six months after orchidectomy. One had a metastasis to the tibia which was treated by deep x-ray therapy and orchidectomy. This showed almost complete recession six months later. The most satisfactory case had a metastasis to the femur, invading the soft parts. Eight months after orchidectomy there was evidence of remarkable healing (shown by roentgenogram and palpation). This is therefore our record to date of the effect of orchidectomy on bone metastasis. In about half there was increase in the bone metastasis. Given time a different picture may present itself.

Stilbestrol. Because castration is not a completely successful antiandrogen, stilbestrol is given in large daily doses (5 mg. daily by mouth) to reinforce the castration effect. In order to determine accurately the effect of stilbestrol, we have used it as the sole treatment in eighteen cases. Of these eighteen patients, seven had bone metastases. Four of the seven showed increase in both the size and number of bone metastases. Two probably developed metastases during the treatment. One had atypical (osteolytic) metastases which in four months showed increase in density. At the present time it is impossible to tell whether this is a healing effect or not. Kohle, Ogden and Gilzoff report one case in which a roentgenogram "showed a marked diminution in the number and extent of the metastatic lesions as compared with previous examination."

But one of our eighteen patients had radon applications to his prostate followed by deep x-ray therapy. One had an orchidectomy at the end of his stilbestrol period (one year and two months). In all of the patients, including one in particular who had a great deal of back pain from dorsal and sacral metastases, pain was successfully controlled by stilbestrol. In this patient the back pain had not been at all affected by deep x-ray therapy. All of these patients gained in weight, one of them twenty pounds in several months. One of them after a year on stilbestrol developed very active skull metastases with much pain in the occipital region and face. In this patient orchidectomy entirely controlled this pain but the patient had a stroke two months after his orchidectomy. In many of the patients the prostate carcinoma became smaller and softer.

In summary, stilbestrol controls pain, causes recession of the prostate growth and improves the general condition but rarely has any effect on the bone metastases. It should therefore be used only in combination with orchidectomy.

Effect of Orchidectomy on Residual Urine: There is very little evidence that orchidectomy has any effect in controlling this symptom. A good many cases with residual urine have had transurethral resection because of imperative symptoms, both to enable the patient to empty his bladder and to obtain a specimen for pathological examination. It is probable that in many cases, once a patient can empty his bladder, orchidectomy is a vital factor in maintaining this power to empty the bladder, because in many patients both after orchidectomy and stilbestrol medication the prostate becomes markedly smaller and softer.

Pre-Orchidectomy Prognosis: Huggins, if I read him correctly believes that the adeno-carcinoma is the type which does best following orchidectomy and that the small cellular carcinoma as a rule does not do well. I can give no data on this point.

Value of Phosphatase in Establishing Prognosis: Sullivan, Gutman and Gutman^s have made these observations: "Castration in every instance (with one explained exception) was followed by early precipit-

ous fall in serum acid phosphatase, often demonstrable after twenty-four hours. On the second post-operative day the mean decline in acid phosphatase was 55 per cent of the pre-operative level." In three cases of our own in which there was no lowering of the acid phosphatase, two died two months after orchidectomy.

Summary of Treatment: We believe that the following suggestions as to treatment of prostatic carcinoma are justified. Orchidectomy and stilbestrol medication should be the treatment in all cases of prostatic carcinoma. This therapy should be preceded by transurethral resection if urinary retention is a dominant factor. Transurethral resection is unnecessary to establish the diagnosis. Aspiration biopsy should be sufficient for this. If the prostatic carcinoma is small, confined to the prostate and peri-prostatic region, radiation of the prostate or the operation of total prostatectomy should be considered.

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PUBLIC HEALTH NEW YORK CITY IN

A Retrospect*

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present a satisfactory retrospect concerning public health in New York City is a difficult assignment, and in the time at my disposal I shall be able to deal briefly with only a few phases of the subject.

1800-1825

During the first quarter of the nineteenth century the city extended to about Canal Street. Shipping and trade were the chief occupations, and the artisans were largely independent workers. Manufacturing played only a minor role, and steam power factories did not become common until the forties and fifties. Housing conditions were favorable; gardens and orchards were common; there were no tenements. In the built-up portions of the city, a private company supplied water through wooden pipes laid beneath the streets; in other parts of the city private wells were in common use. Outdoor privies were the rule, and they were built over water-tight vaults which were emptied at intervals by the scavenger. Water closets did not come into use until after the introduction of Croton water in 1842. Judging from what reports, etc., are available, New York appears to have been a reasonably clean and tidy town during the first quarter of the nineteenth century.1 The general death rate from all causes was about 25 per 1000 and the infant mortality ranged between 120 and 140 per 1000 live births. This first quarter of the century was relatively free of serious epidemics, though yellow fever appeared in 1805 and again in 1822.

1825-1850

The second quarter brought profound changes. The population growth became accelerated. With the introduction of steam power, fac-

^{*} Read November 4, 1942 before the Section of Historical and Cultural Medicine of The New York Academy of Medicine. † On June 1, 1943 the author completes 39 years of distinguished service in public health work. Ed.

tories multiplied, and these attracted workers to the city. Immigration from Europe increased rapidly, at first from Ireland and during the late forties from Germany and other continental countries. The competition of the ever increasing immigrants lowered all standards of living. Wages, especially after the panic of 1837, were reduced, and again reduced. The housing situation became acute. To relieve the overcrowding the cheapest kinds of houses were built. Cellars were used as living quarters. All in all conditions became more and more insanitary.

In 1832 a severe epidemic of cholera caused 3500 deaths and a recurrence in 1834 carried off nearly 1000 victims. Finally just before the close of this second quarter, in 1849 cholera again ravaged the city causing over 5000 deaths. The first appearance of cholera, in 1832 gave renewed impetus to plans for a satisfactory and sufficient water supply, and these were finally carried through successfully in 1842 when the Coton Aqueduct was opened. An account of the many difficulties attending this important undertaking will be found in the August 1942 issue of the *Quarterly Bulletin* of the New York City Health Department.

The insanitary conditions which marked this second quarter are reflected in the steady increase in the infant mortality rate. By 1850 this had climbed to 180 per 1000 live births.²

The second quarter also marked the beginning of the campaign for pure milk for the people of this city. Perhaps you know that this was a by-product of a great temperance campaign, whose prime mover was a Mr. Robert Hartley. He soon discovered that distillers made money by selling to dairymen the mash remaining after whiskey was made. He investigated the cow stables which adjoined the distilleries, and discovered conditions so insanitary that it is hard to believe them today. Largely as a result of Mr. Hartley's exposé, The New York Academy of Medicine in 1848 appointed a committee to look into the milk situation. Despite the efforts of the Academy, and of other public spirited citizens, notably Frank Leslie, the publisher, it was not until nearly fifty years later that a wholesome milk supply was provided for the people of this city.

1850-1875

We return now to the beginning of the third quarter of the ninetcenth century. The built up portions of the city had meantime extended rapidly. There was considerable dissatisfaction concerning the filthy condition of the streets, and with the city's health administration. In 1851 an epidemic of smallpox caused 562 deaths and three years later cholera claimed over 2500 victims, and 1137 in 1866. Smallpox continued to ravage the city causing 664 deaths in 1865; 1662 in 1872 and 1889 in 1875. Even yellow fever reappeared, though there were only 9 deaths, in 1870. A committee of prominent citizens became active during the fifties and sixties, a committee in which Dr. Stephen Smith took a leading part. A detailed sanitary survey carried on under the auspices of this committee revealed revolting insanitary conditions. Filthy streets, filthy stables and cow barns, wretched slum housing, cellar dwellings, backyard tenements without light or ventilation, outdoor, insanitary privies, adulterated milk supplies, and generally high death rates. You can read it all in Stephen Smith's book The City that Was.³

I can perhaps add a bit of evidence of interest. Many of you may remember my friend the late Dr. William H. Guilfoy, formerly Registrar of Records. Dr. Guilfoy was born on the lower West Side, not far from Washington Market, in 1859. He told me that as a young lad, on rainy days he would hurry home from school, arm himself with a broom, station himself at near-by Broadway and there offer to sweep a path through the muck and filth so that a person could cross the street. "And many a nickel I picked up in this way."

In the early sixties the built-up portion of the city embraced about eight square miles and the population numbered nearly a million. Besides the insanitary conditions just mentioned there were a vast number of special nuisances. Thus there were nearly 200 slaughter houses, many of them in the most densely populated districts. To these places droves of cattle, hogs and sheep were constantly driven rendering the streets extremely filthy not only with animal excreta, but with the blood and refuse flowing from the slaughter houses. In certain populous sections there were establishments for fat and bone boiling, for cleansing entrails and curing tripe. The numerous stables and cow barns have already been mentioned. They brought the additional nuisance of manure heaps and the carting of this manure through the streets. In this connection some pictures taken from the Report of the Citizens' Committee may be of interest.⁴

It may be well, at this point to call attention to the great social and sanitary reforms inaugurated in England during the forties, fifties and



Fig. 1—The vicinity of a slaughter house during the 1850's. Note the public school.

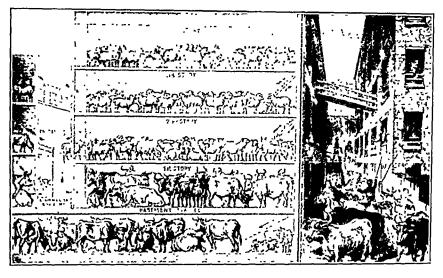


Fig. 2-Plan of a slaughter house. From the Report of Citizens' Association.

sixties of the last century. These may be said to have had their beginning in the reports published by John Howard concerning conditions in prisons, hospitals and lazarettos of Europe 1777-1789. But it was the repeated occurrence of devastating epidemics of cholera during the thirties which gave real impetus to the movement and here we find Edwin Chadwick, Florence Nightingale, John Simon, John Snow, Edmund Parkes, William Budd and the statistician William Farr making

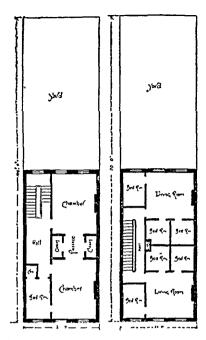


Fig. 3—A private dwelling remodelled into a tenement. One floor rearranged for two families. Inside bedrooms without light or ventilation.

very valuable contributions. The influence of these reforms manifested itself in this country in reforms urged in Massachusetts by Lemuel Shattuck, and in New York by the remarkable achievements of Stephen Smith and Dorman B. Eaton in connection with the work of the Citizens' Committee already mentioned.⁴

Let me return, therefore, to the accomplishments of this committee, for they became the basis of sanitary legislation throughout the country.

Prior to 1866 there were in this city four separate authorities devoted to the conservation of public health. Quoting from Stephen Smith,³ there were:

"First, the Board of Health, composed of the Aldermen and Mayor. When this body was organized as a Board of Health it had supreme power, both in the abatement of nuisance and the expenditure of money. So much and so justly was this board feared, that Fernando Wood, while Mayor, refused to call it into existence during an epidemic of cholera, declaring that the Board of Health was more to be feared than the pestilence.

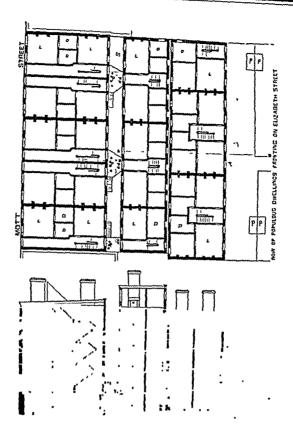


Fig. 4—Tenements occupying nearly the entire lot. One building faces the street at the left. Back of this is a narrow court, and then comes the rear tenement on the same lot, having windows only to the court.

Note a similar rear tenement on the lot in the year

"Second, the Commissioners of Health, composed of the Mayor and the Recorder, the City Inspector, the Health Commissioner, the Resident Physician, the Port Health Officer. This body had no adequate power and was perfectly useless both for good and evil.

. "Third, the Resident Physician, whose duties were limited to visiting the sick poor.

"Fourth, the City Inspector, a most formidable official politically, for he had the right to expend annually \$1,000,000 without "let or hindrance." His jurisdiction extended to the cleaning of the streets, gathering vital statistics, and preserving the public health by the appointment of health wardens for each ward.

"The committee's investigation showed that this department, the only one which actually exercised public health functions, was per-

meated with corruption, ignorance, and venality. The City Inspector was the lowest type of ward politician, the vital statistics were crude and unreliable, there was no pretense of cleaning the streets, and the health wardens were for the most part keepers of saloons."

As I read over the annual reports of the various City Inspectors,⁵ I believe that Stephen Smith was a little unjust. Some of the officials appear to have been alert and competent health officers. For example John Pintard who served from 1804 to 1810 made recommendations on the following: Ample supply of pure potable water; drainage of low marsh land; construction of common sewers; the interment of dead bodies within the city; prohibiting the habitation of damp cellars; providing increased accommodations at Bellevue Hospital; enforcement of accurate returns of death; and regulations regarding the quarantine of vessels coming from southern ports during the months of July, August and September.

City Inspector Dunnell in 1838 was the first to advocate maintenance of a registry of births.

City Inspector Griscom in 1842 gives a review of the sanitary condition of the city, together with many excellent recommendations. He demands that all certificates of death give data concerning the occupation of the deceased, so that industrial health hazards may be discovered. Finally we find him suggesting the taking of regular meteorological observations and the careful keeping of weather records.

City Inspector Archer, 1845 and 1846, demands the establishment of municipal slaughter houses, and of a hospital for pestilential and epidemic diseases. He succeeds in the enactment of a law requiring birth registration. Since it carried no penalty it proved ineffective.

City Inspector Downing (1852-1854 incl.) publishes excellent annual reports dealing with sanitary matters and vital statistics. He advocates the establishment of two bureaus, a Bureau of Sanitary Inspection and a Bureau of Registry and Statistics. The report for 1853 gives the text of an improved Birth, Marriage and Death Registration Act which Downing succeeded in having enacted.

City Inspector Delevan in his report for 1859 issues a blast at the street railway companies for the insanitary condition and overcrowding of the cars. In 1860 he urges the city to limit the number of persons living in a tenement room. Delevan appears to have been the first city inspector to advocate that a successful vaccination be required before

a child should be allowed to enter school.

It is apparent that these City Inspectors had an intelligent grasp of the health problems confronting the city, and it is likely that the chief fault was the failure of the Legislature to arm them with sufficient powers. I trust that future historians will erase the stigma placed upon these city officials by the report of the Citizens' Committee.

In an effort to correct the situation disclosed by the survey of the Citizens' Committee, health bills were repeatedly sent to the Legislature, only to be rejected because of the powerful influence of the City Inspector whose \$1,000,000 was expended freely in the lobby at Albany. The Citizens' Committee thereupon enlisted the services of Mr. Dorman B. Eaton to draft suitable legislation to be presented to the state legislature. Mr. Eaton fortunately proved to be one of the few citizens who had kept pace with the progress of sanitary reforms in England and entered fully into the spirit of the great movement that for a quarter of a century had agitated the people of that country.

When the draft of the legislation came from the hands of Mr. Eaton it was evident that he had made a thorough study of the English health code. It provided for a Board of Health armed with extraordinary powers. According to Mr. Eaton a board of health should make its own laws, and sit in judgement on its own acts. He believed, however, that no legislature would pass a bill containing such powers if these powers were made a prominent feature of the Bill. For that reason he had adopted that involved expression peculiar to English law which required a judicial interpretation to determine the precise meaning.

Presented to the Legislature of 1865 the bill finally failed of passage. Thereupon the Citizens' Committee inaugurated a campaign to defeat for re-election those legislators who had voted against the bill. In this the New York Times rendered great service. Seventeen former members of the legislature failed to be renominated. In the new legislature the bill promptly passed both houses early in the session of 1866, and in March the Metropolitan Board of Health was organized.

I have dwelt with some detail on Eaton's work because its influence has not been sufficiently recognized by our medical historians. Garrison, for example in speaking of the public health movement in those days says: "In the United States, the leading prime movers of public hygiene were Lemuel Shattuck, of Boston, who by his famous report to the Massachusetts Sanitary Commission (1850) did for New England what

Chadwick, Farr and Simon had done for England; John Shaw Billings, who strove to give their ideas a nation-wide application, while Stephen Smith, Hermann M. Biggs, William H. Park in New York, Baker in Michigan, Dixon in Pennsylvania, Welch and Fulton in Maryland, Folsom and Sedgwick in Massachusetts, Joseph Jones in Louisiana, Winslow in Connecticut and Kober in the District of Columbia did yeoman service for their several states." Not even a mention here of Eaton.

You may be interested in an excerpt from a letter written to me in 1930 by our beloved "Popsy Welch." ⁷ "Lemuel Shattuck," he writes, "is called by Whipple, Winslow, Newsholme and others, the Edwin Chadwick of America, and perhaps in a sense he is, but his remarkable writings were without perceptible influence at the time, were based largely on Chadwick and other writers, and, above all were not associated with any such overwhelming presentation of facts as in the case of Chadwick. Dorman B. Eaton is more deservedly the Chadwick of America if achievement and influence as well as literary production be considered."

When the Metropolitan Board of Health was established in 1866 the Act provided for two bureaus, one the bureau of vital statistics, the other the sanitary bureau. All the activities of the new Department of Health, excepting only those dealing with the registration, tabulation and analysis of the records of births, deaths and marriages, were carried on by the sanitary bureau, whose field staff, the sanitary inspectors, were all physicians on part time service. They supervised isolation and quarantine, investigated cases of contagious diseases, performed vaccinations, made sanitary inspections to detect nuisances, etc. The reports of the Health Department of those days devote much attention to environmental sanitation,8,9 to housing, offensive trades, removal of night soil, sewerage and plumbing. As director of the Department's chemical laboratory, Prof. Charles F. Chandler did outstanding work in detecting the adulteration of milk and other foods. Elisha Harris, as Registrar, introduced order into the mortality statistics, calling special attention to the frightful ravages of cholera infantum.

1875-1900

We come now to the most interesting era in the public health history of the city, the fourth quarter of the nineteenth century, for it was during this period that Pasteur, Koch and their pupils showed that

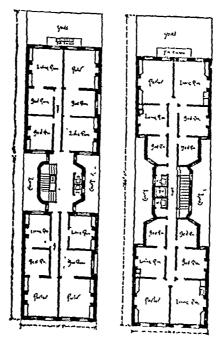


Fig. 5—One of the worst types of tenements, still in existence, in the so-called "dumb-bell" plan. Note that in 1879 this was awarded a prize. There are four families on a floor. Bedrooms receive light and ventilation only from a narrow shaft between the buildings.

a large number of diseases were caused by specific microörganisms. The earliest practical application of this new knowledge was made by Lister, in the field of surgery. Next, and of equal importance was its application in the field of sanitation and preventive medicine, and here the undisputed leader was Hermann M. Biggs. ¹⁰ In 1885 he had been made instructor in bacteriology in the Bellevue Medical College, the course being given in the then new Carnegie Laboratory in East 26th Street. The laboratory was officially directed by Janeway and Dennis, but actually Biggs did the work. In October 1887 the steamship "Brittania" had arrived at the New York Quarantine Station from Marseilles and Naples with a history of three deaths among the steerage passengers. Two more passengers died while the ship lay at quarantine, and from one of these cases, suspected to have been cholera, culture tubes inoculated from the intestinal contents were brought to the laboratory.

The examination by three independent observers, Prudden, Biggs and Weeks, showed that the disease was true cholera. All the immigrants

were then removed from the vessel, and several days later a number of other cases of cholera occurred among them. At this time Biggs had served with Janeway and others as a member of a conference committee between the Department of Health and The New York Academy of Medicine, created primarily to discuss the cholera situation. In 1888 Janeway, Prudden, Biggs and H. P. Loomis were appointed Consulting Pathologists to the Department of Health.

On several occasions Biggs suggested to Joseph D. Bryant, who was a power in the Board of Health, the creation of a Division of Pathology, Bacteriology and Disinfection, and funds for such a division were inserted in several of the budget requests, but were denied. Then, in August, 1892, when the city was in a panic because of the arrival at New York of several cholera-laden ships from Hamburg, the Board of Health secured an emergency appropriation for the establishment of a bacteriological laboratory to diagnose cholera. Dr. Biggs was placed in charge and given the title "Chief of the Division of Pathology, Bacteriology and Disinfection."

Similar emergency laboratories had been set up about that time in Hamburg, Bremen, Berlin and London, so that there was apparently nothing remarkable about New York City's action. Nevertheless it was an epoch making event, for whereas the several European laboratories were discontinued after the cholera emergency had passed, the laboratory established by the New York City Board of Health was continued as an integral part of the Health Department's services to practicing physicians. In fact, on the day the laboratory was opened, September 1, 1892, Biggs announced that it would be able to help physicians in the differential diagnosis of obscure cases; such as diphtheria and follicular tonsillitis. He also mentioned its value in the bacteriological examination of drinking water, milk and other foods, and spoke of bacteriologic research.

Biggs lost no time in carrying this program into effect. In April 1893 he brought Dr. William H. Park into the laboratory and assigned to him the problem of working out a practicable method of aiding physicians in the diagnosis of diphtheria. Within a short time Park had devised the diagnostic outfits for making throat cultures, and then the laboratory inaugurated the plan of having supplies of these diagnostic outfits available to physicians in conveniently located drug stores. Throat cultures left by the physicians at these drug stores stations

were collected daily by a messenger from the laboratory. After incubation overnight, they were examined early in the next day and the result telephoned to the attending physician. In January 1894 the laboratory offered to examine sputum for tubercle bacilli, and made suitable sputum bottles available at the drug store stations. Soon after, the laboratory offered to examine pus smears for gonococci and blood smears for malaria, also specimens of blood for the Widal reaction for the diagnosis of typhoid fever.

How marked the influence of the first bacteriologic diagnostic laboratory was on public health methods throughout the United States is well indicated by the following sentence taken from the preface of the first edition of Park's Bacteriology in Medicine and Surgery¹¹ published in 1899:

"The methods used in the laboratory for the isolation and identification of the typhoid, tubercle, and diphtheria bacilli have been given with special fulness, as the bacteriological examinations of the discharges of persons suspected to have typhoid fever, tuberculosis, or diphtheria are now generally made for those bacteria in the laboratories of the health departments of even the smaller cities, because of the manifest importance to the public of knowing where such sources of infection exist."

That is to say, within less than seven years the health departments of even the smaller cities were using the new tool conceived by Biggs when he opened the emergency cholera laboratory in 1892! The same opportunity was presented to the European cities mentioned above, but only Biggs had the vision to grasp it.

A valuable collateral service which can be rendered by the diagnostic laboratory of a health department, a service clearly recognized and promptly made use of by Biggs, is the securing of notification of disease. Two instances will suffice to show how effectively this was utilized. In the face of much opposition Biggs in 1894 had prevailed upon the Board of Health to make tuberculosis reportable. Hospitals and other institutions were ordered to report all cases, while private physicians were requested to do so. At the same time the diagnostic laboratory offered to make examinations of sputum for tubercle bacilli. This diagnostic aid was appreciated by physicians and the specimens submitted soon made up a substantial proportion of the cases of tuberculosis reported to the Health Department. In similar fashion eighteen years later,

in 1912, Biggs overcame the violent opposition to the reporting of venereal diseases. In that instance the laboratory announced that it would make Wassermann blood tests free of charge, a startling offer at that time for private laboratories were charging five or ten dollars for such tests.

In 1893, the year that Park had begun to work on diphtheria in the Health Department's laboratory, Behring announced the discovery of diphtheria antitoxin. At an international medical congress held in Budapest in 1894, several outstanding pediatrists were able to report their clinical experiences with this new therapeutic agent. Biggs, who attended the congress, was so impressed that he cabled Park to immunize horses and start making diphtheria antitoxin. So it came that the laboratory established less than two years before, embarked on a large additional field of activity, while still expanding the diagnostic service.

The diphtheria antitoxin produced by Park proved much more potent than any produced by Behring in Berlin or by Roux in Paris. Within a short time the laboratory received urgent pleas from the health departments of other American cities that they be permitted to purchase Park's product. Here, once again, Biggs showed his genius. Since there was no authority for permitting the city to go into serum production as a business, he secured the passage of an act by the State Legislature (1895), authorizing the New York City Department of Health to undertake the manufacture of serums and vaccines for the people of the city, and to sell any surplus products. The money derived from such sale was to be deposited in a special account known as "The Antitoxin Fund" and to be at the disposal of the Board of Health for research studies on serums and vaccines. For many years Park and his associates were kept busy manufacturing "surplus" products for sale to other cities; and the income thus obtained quickly enabled the laboratory to become one of the world's foremost research laboratories in the field of public health.12

Although officially only director of the Division of Pathology, Bacteriology and Disinfection, and a subordinate of the Sanitary Superintendent, Biggs since his appointment to this position in 1892, was a real power in the Health Department. In 1894 he inaugurated the pioneer campaign for the administrative control of tuberculosis, and gradually organized a program which was subsequently followed by health authorities throughout the world. In 1896 he was influential in having the

Board of Health adopt a section of the sanitary code prohibiting the sale of milk in the City of New York except under a permit and subject to the rules and regulations of said board. This may be said to mark the beginning of the modern effective system of controlling the quality of its milk supply. In 1897 Biggs was instrumental in inaugurating a system of school medical inspection, 150 part-time medical inspectors being added to the Health Department's staff for this purpose. In that year, also, the reporting of tuberculosis was made compulsory, even for private physicians. The formation of Greater New York in 1898 brings to a close this account of health activities during the fourth quarter of the nineteenth century.

SINCE 1900

The election in 1901 brought a reform administration into power with Seth Low as Mayor. The new mayor asked Biggs to accept appointment as Commissioner of Health, but Biggs feeling that he could not undertake the responsibilities of full administrative authority declined. He accepted, instead, appointment as the "General Medical Officer," a position which was largely free from administrative detail but which involved the development of all the broader policies of the Department. In this capacity he served for twelve years, under Lederle, under Darlington and under Lederle again, always behind the scenes as the real directive force, formulating and guiding the work of the Health Department. In fact as we look back to Biggs' association with the Department from 1892 to 1914 we realize that it was the golden era in the public health history of the city.

In 1902 as a result of experimental studies made by Miss Lillian Wald, a staff of seventeen municipal school nurses was established, the first to be employed in the United States. In 1903 the first tuberculosis

nurses were appointed.

During 1903-4 a study by Park and Holt showed conclusively that there was no specific germ of "cholera infantum" and that summer diarrhea of infants was principally due to an excessive number of ordinary dirt bacteria in milk fed to infants.

In 1904 a commission appointed by the Board of Health for the study of respiratory diseases inaugurated the first attempt to deal ef-

fectively with pneumonia.

In the winter of 1904-5 a severe epidemic of meningitis resulted in

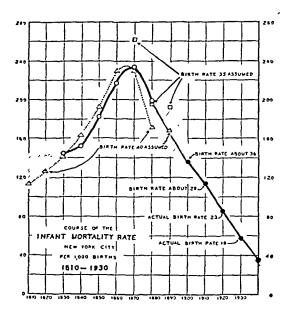


Fig. 6—Infant mortality in New York City 1910-1940. The rates are per 1000 live births. Small circles indicate the rate based on estimates of births arrived at from the census population under five.

important contributions to our knowledge of that disease.

In 1905 the Department of Health inaugurated the routine examination of school children for physical defects. In that year, also, on the recommendation by Dr. Doty, health officer of the port, extensive drainage work was begun on the marsh lands of Staten Island for the elimination of mosquitoes.

In 1906 country inspection of the city's milk supply was begun. The Board of Health also amended the sanitary code so as to class as adulterated, milk which was kept at a temperature above 50°F. Two years later milk was also defined as adulterated if it contained an excessive number of bacteria. In 1906 the first municipal tuberculosis sanatorium was established by the Health Department at Otisville.

In 1907 an extensive outbreak of typhoid fever, traced to pollution of the Croton water led to a thorough survey of health conditions in the watershed, and disclosed serious defects in state health administration. This year saw also the registration of the first carrier, "Typhoid Mary," and her forcible detention by the Board of Health as a menace to the public health.

In 1908 the first division of child hygiene was established, Dr. S.

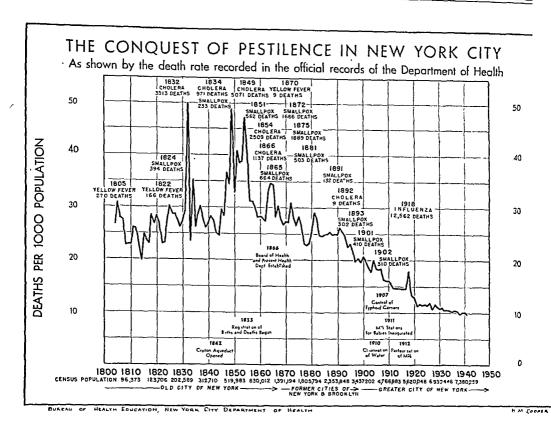


Fig. 7—Course of New York City's general death rate 1804-1940. It is probable that the rate during the first half of the past century were somewhat higher than indicated, because of incomplete reporting.

Josephine Baker being placed in charge.14

In 1911 the first fifteen baby health stations were established. In 1912 forty more were added.

In 1911 the Board of Health introduced the grading of the milk supply, a system which remained in force until 1941. Pasteurization of all milk was enacted in 1913.

In 1912 the Health Department was reorganized into eight distinct bureaus, a ninth, the Bureau of Health Education being added in 1914. In that year, also, Biggs drew attention to the diseases of later life as a problem demanding the attention of health administrators, and had your speaker collect statistical data pertaining to this subject.¹⁵

Early in December 1913 Biggs resigned as General Medical Officer and on January 1, 1914, was appointed State Commissioner of Health. Under the new city Commissioner of Health, Dr. S. S. Goldwater, the position of General Medical Officer was abolished.

Goldwater's administration (January 1, 1914 to November 1, 1915) marks the first attempt at organizing health administration on a district basis, an experimental district health center being established in December 1914. Subsequently, under Goldwater's successor Haven Emerson, several additional experimental health centers were established. All of them were, however, disbanded after the change of administration in 1918.

Other outstanding features of Goldwater's administration were:

The creation of a Division of Statistical Research, of a Division of Industrial Hygiene, and of a Bureau of Health Education.

A tabulation and analysis of vital statistics by sanitary areas made by Guilfoy and Wynne.

Provision for the annual physical examination of foodhandlers.

Under the administration of Commissioner Haven Emerson (from late in 1915 to 1918), the World War placed considerable burdens on the Department of Health, depleting its medical and nursing staff and making extraordinary demands on the laboratory in order to supply the army with serums and vaccines.

In 1916 the city experienced the most extensive and most serious epidemic of poliomyelitis ever recorded, either before or since.

The same is true of the pandemic of influenza beginning in the fall of 1918.

Under the administration of Commissioner Copeland and his successor Commissioner Monaghan, Dr. Wynne in coöperation with Dr. Arthur W. Bingham, President of the Medical Board of the Willard Parker Hospital, effected a thorough reorganization of the Health Department's contagious disease hospitals, introducing the cubicle system, aseptic nursing and other important reforms. Dr. Wynne remained in charge of this hospital service until his appointment as Commissioner of Health in 1928.

Mention should also be made of the remarkably effective campaign carried on against diphtheria under the leadership of Commissioner Shirley W. Wynne. During the year immediately before this campaign began there were 642 deaths from diphtheria. Last year, in 1941, there were only 10!

Under Dr. Wynne there were also begun tuberculosis case-finding by means of extensive chest x-ray surveys, and the consultation service for suspected cases of tuberculosis under the care of private physicians. and for suspected cases of venereal disease.

Finally it was Dr. Wynne who initiated the present program of District Health Administration which has been so extensively developed by Commissioner Rice under Mayor La Guardia's administration.

Before closing this retrospect I should like to mention the invaluable aid extended to the Department of Health by The New York Academy of Medicine almost since its organization in 1847. I referred to such help in speaking of the beginnings of the campaign to provide pure milk for the people of this city. Ever since then, but particularly since the formation of the Academy's Committee on Public Health in 1911, the Department has had invaluable assistance in its efforts to promote the public health. We are indeed very grateful.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETING

DECEMBER 3-The New York Academy of of Medicine. Executive session-Reading of the minutes. ¶ Papers of the evening, scientific program in cooperation with the Section of Genito-Urinary Surgery. Prostatic carcinoma-a) Diagnosis of prostatic carcinoma and its metastases, including value of phosphatase determinations, Charles B. Huggins, Professor of Surgery, University of Chicago; b] Treatment of prostatic carcinoma, Benjamin S. Barringer, Attending Surgeon, Department of Urology, Memorial Hospital. ¶ Report on election of Fellows. Report on election of Academy officers.

December 17—The Harvey Society in affiliation with The New York Academy of Medicine. The Third Harvey Lecture, "Poliomyelitis," John R. Paul, Professor of Preventive Medicine, Yale University School of Medicine.

York Academy of Medicine. ¶ Executive session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. ¶ Presentation of Annual Reports (to be read by title), The Council, The Trustees, The Treasurer, Committees. ¶ Address of the retiring president—Malcolm Goodridge. ¶ Address of the incoming president—Arthur F. Chace. ¶ Paper of the evening—Scientific program in cooperation with the Section of Surgery, and the New York Surgical Society. Shock—a major war problem in medicine and surgery—

Alfred Blalock, Professor of Surgery, Johns Hopkins University School of Medicine. ¶ Report on election of Fellows.

JANUARY 21—The Harvey Society in affiliation with The New York Academy of Medicine. The Fourth Harvey Lecture, "Studies on the Pathological Physiology of Cushing's Syndrome," Fuller Albright, Assistant Professor of Medicine, Harvard Medical School.

SECTION MEETINGS

DECEMBER 1—Dermatology and Syphilology.

¶ Presentation of cases—a] From The
New York University College of Medicine; b] Miscellaneous cases. ¶ Discussion. ¶ Executive session.

DECEMBER 4-Surgery. | Reading of the minutes. ¶ Case presentations—a] Cases illustrating the first paper of the evening, J. William Hinton. b] Stenosing ulcer of the duodenum with severe hemorrhage, treated by gastrojejunostomy, William A. Fraser. Papers of the evening-The intractable duodenal ulcer; evaluation of surgical procedures, J. William Hinton, discussion opened by Felix de Amesti, Santiago, Chile, Professor of Surgery, University of Santiago. b] Injuries to the larynx and trachea, Robert L. Nach (by invitation) and Milton Rothman. ¶ General discussion opened by Francis X. Timoney. ¶ Executive session.

DECEMBER 8-Combined Meeting. New York

Neurological Society and the Section of Neurology and Psychiatry, C Papers of the evening-al The use of focused ultra-sound waves for the production of transcranial focal brain lesions, John G. Lynn (by invitation), Tracy J. Putnam, discussion by Harold G. Wolff, Charles Davison; blA psychiatric study of forty torpedoed seamen, Lawrence S. Kubic, Leo Stone (by invitation), Sydney Margoline (by invitation), Mark Kanzer (by invitation), discussion by Daniel Blain, Howard W. Potter; cl The role of instinct in human behavior, J. Marmor, discussion by Israel S. Wechsler, A. Kardiner.

Dicimin 10—Pediatrics, ¶ Reading of the minutes. ¶ Presentation of cases—a] A case illustrating teaching of body mechanics, Miriam T. Sweeney (by invitation); b] A case of weak feet and poor posture, Beekett Howarth, ¶ Papers of the evening—Discussion of posture and training, William T. Green, Children's Hospital, Boston (by invitation), Beckett Howorth, ¶ General discussion.

Dramma 15—Medicine, § Executive session—Reading of the minutes, § Papers of the evening—Diseases of the liver and bihary system—a] Treatment of cirrhosis, Arthur J. Patek, Jr. (by invitation); b] Eleven years' experience with thorotrast hepatosplenography, Wallace M Yater (by invitation); c] The conservative treatment of gallbladder and biliary tract disease, Carl H. Greene, discussion by Franklin M. Hanger, Reuben Ottenberg, Leopold Lichtwitz.

Dicimin 16—Otolaryngology, § Reading of the minutes. § Paper of the evening— Tumors of the nasal sinuses, LeRoy A. Schall, Boston, Mass. (by invitation), discussion, John D. Kernan, Maurice Lenz, Hayes Martin, § General discussion, § Executive session.

Genito-Urinary Surgery-The Section of Genito-Urinary Surgery did not hold its regular meeting on December 16, as it combined its scientific program with that of the Stated Meeting on December 3.

December 18—Orthopedic Surgery, Reading of the minutes, Papers of the evening—a] Plastic surgery in orthopedic cases, Yolande H. Huber, discussion by Leo Mayer; b] Massive skin plastics for release of orthopedic deformities, David M. Bosworth, discussion by Joseph B. L'Episcopo; c] Skin grafting of war wounds, John M. Converse (by invitation). ¶ General discussion. ¶ Executive session.

December 21-Ophthalmology, ¶ Instruction hour 7:30 to 8:00 o'clock, moving picture and exhibit, Henry Minsky, § Executive session-Reading of the minutes. In memoriam—Samuel P. Oast, by Clyde McDannald, ¶ Papers of the evening-Pathology of unsuccessful operations for cataract, Theodore L. Terry (by invitation), discussion by John M. McLean, ¶ New instruments, apparatus -New atraumatic catgut suture for use in cataract surgery, Wendell Hughes, Experimental studies-Hunter Romaine (by invitation), discussion by Loren P. Guy, ¶ Presentation of cases—a] Tuberous sclerosis, Elizabeth F. Constantine (by invitation), discussion by Thomas I. Hoen; b] Cyst of the iris, Herbert Katzin (by invitation), discussion by Kaufman Schlivek.

December 22-Obstetrics and Gynecology. Executive session-Reading of the minutes. Case reports-Ruptured uterus-an account of recent cases and brief review of cases for the past ten years at the New York Lving-In Hospital, Earl B. King (by invitation). Papers of the evening-alEvaluation of the pregnandiol complex as an index of ovarian and uterine function, determined by the Venning-Browne test, Samuel L. Siegler; b] The effect of mixed conjugated estrogens from pregnant mares' urine (premarin) in the treatment of menopause, Theodore Neustaedter. General discussion.

JANUARY 5—Dermatology and Syphilology.

¶ Presentation of cases—a] From Vanderbilt Clinic and Presbyterian Hospital, College of Physicians and Surgeons.
b] Miscellaneous cases. ¶ Discussion.

¶ Executive session.

January 12—Neurology and Psychiatry.

Papers of the evening—a] The endocrine dysergias and anergias, Otto Marburg (by invitation), discussion by Bernard Sachs, Tracy J. Putnam; b] Sex and chemistry of the brain, Arthur Weil, discussion by Harry Sobotka, Richard J. Block (by invitation); c] War neurosis, John Frosch (by invitation), discussion by Sandor Rado, A. Kardiner. ¶ Executive session.

JANUARY 13-Historical and Cultural Medicine. ¶ Executive session-Appointment of nominating committee. Papers of the evening-Vesalius Celebration, honoring the Quadricentenary of the publication of De Humani Corporis Fabrica (1543)-a] "Andreas Vesalius, Professor in The Medical School in Padua,' Arturo Castiglioni (by invitation); b] "The Position of Vesalius in The History of Medicine," Henry E. Sigerist (by invitation), discussion by James F. McDonald, Gregory Zilboorg, Mr. Wilniam M. Ivins, Jr. (by invitation). ¶ Exhibit of books of Andreas Vesalius, from the library of the Academy.

JANUARY 14-Pediatrics. ¶ Reading of the minutes. [Papers of the evening-a] A simplified method of making infant formulae, Katharine K. Merritt, Irene Waters, A.B. (by invitation), Emma Mike, B.S. (by invitation), discussion by Donovan J. McCune; b] The initial nasopharyngeal flora of infants in relation to ultra violet radiation, J. C. Torrey (by invitation), Martha Reese (by invitation), discussion by Samuel Z. Levine; c] New problems in the treatment of pneumonia, Rosa Lee Nemir (by invitation), discussion by Jesse G. M. Bullowa (read by Gertrude Weiss), Wheelan D. Sutliff (by invitation).

JANUARY 18-Ophthalmology. & Instruction hour 7:00 to 8:15 o'clock; motion pictures-surgical operations on the eyes, Institute of Ophthalmology, Manhattan Eve. Ear & Throat Hospital, New York Eye & Ear Infirmary. § Executive session-Reading of the minutes. § Papers of the evening-a] Military ophthalmology, William Thornwall Davis (by invitation); b] Penicillin and sulfadiazine treatment of experimental intraocular infection with pneumococcus, Ludwig . Sallmann (by invitation), discussion by Karl Meyer (by invitation); c] The topography of the orbit with particular reference to retrobulbar injection, Robert Lambert, Virginia Lubkin (by invitation). ¶ Presentation of cases-al Harada's disease (?) -report of a case, I. Givner, discussion by Ludwig Sallmann (by invitation).

Orthopedic Surgery. Due to the annual meeting of the American Academy of Orthopedic Surgeons in Chicago on January 15, the regular meeting of the Section was not held.

20 - Genito - Urinary Surgery. JANUARY Reading of the minutes. Case reports-a] Rectourethral fistula with perirectal abscess, C. V. Burt (by invitation); b] Embryonic polycystic kidney with autopsy findings, Vincent Corrigan (by invitation); c) Fused unascended kidneys with changes in pregnancy, Simon A. Beisler; d] Polycystic kidneys, Ralph C. Yeaw (by invitation). Paper of the evening-Spot test for rapid analysis of calculi, Julius H. Winer, Lt., M.C., A.U.S. (by invitation), M. R. Mattice. ¶ General discussion. ¶ Executive session.

January 20—Otolaryngology. Reading of the minutes. Papers of the evening—all Pathology of petrositis, report of three cases with lantern slide demonstration, Andrew A. Eggston, discussion by Wesley C. Bowers, John R. Page, Dorothy Wolff, St. Louis, Mo. (by invitation); bl Surgical treatment of carcinoma of

the larynx, presentation of cases, moving picture, Maxwell Ryan (by invitation). ¶ General discussion. ¶ Executive session.

JANUARY 21-Joint Scientific Session, Medicine and the New York Heart Association, Heart Committee of the New York Tuberculosis and Health Association. ¶ Annual report of the New York Heart Association, Edwin P. Maynard, Jr. Papers of the evening-al Cardiac problems in wartime, Paul D. White (by invitation), Physician, Massachusetts General Hospital, Lecturer in Medicine; b] Vascular and neurological lesions of the extremities in survivors of shipwreck, James C. White, Commander (MC) U.S.N.R., Neurosurgical Service, U. S. Naval Hospital, Chelsea, Mass. and Massachusetts General Hospital; c] Experiences with various cardiac problems in the present war, Arthur M. Master, Commander (MC) U.S.N.R., Cardiologist, National Naval Medical Center, Bethesda, Maryland.

JANUARY 26—Section of Obstetrics and Gynecology. [Executive session—reading of the minutes. [Case reports—Failure of corpus luteum medication in an Rn negative patient having two consecutive miscarriages—Robert S. Millen. [Papers of the evening—a] Study of edema and toxemia of late pregnancy in relation to sodium and potassium imbalance—Thomas J. Parks (by invitation); b] Treatment for delayed menstruation combined with a test for early pregnancy, Haig Carpatyan (by invitation). [General discussion.

AFFILIATED SOCIETIES

December 10—New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Paper of the evening—The chronology of mammary

cancer, James Ewing. ¶ Executive session.

December 21-New York Roentgen Society in affiliation with The New York Academy of Medicine, ¶ Papers of the evening-a] The influence of hormonal changes on carcinoma metastases to bone, Helen Q. Woodard (by invitation), discussion by Alfred Hocker (by invitation); b] Radioactive isotopes in the determination of circulating erythrocyte volume, Robert Anderson (by invitation), discussion by Lloyd Craver (by invitation); c] Dosage calculations for various combinations of parametrial needles with intracervical tandems, James Nolan (by invitation), discussion, Gray Twombley (by invitation). ¶ Executive session.

January 18—New York Roentgen Society in affiliation with The New York Academy of Medicine. Past presidents' program. [Papers of the evening—a] Two cases of ileocaecal carcinoma, Harry M. Imboden; h] A case of mediastinal tumor, presumably lymphosarcoma, Ross Golden; c] Two cases of uncommon chest lesions in newborn infants, Robert E. Pound; d] A non-traumatic diverticulum of the prostatic urethra, A. L. Loomis Bell. [Discussion open to members. [Executive session.

JANUARY 28—New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Presentation of cases—a | A case of cystic fibrosis of the pancreas in an infant, Marcel Palmer (by invitation); b | A case of generalized thromboangiitis, Thomas G. Morrione (by invitation). ¶ Papers of the evening—a | Concretions in the pituitary of the fetus and the newborn, Alfred Plaut; b | Diagnosis of chondrosarcoma of bone, Louis Lichtenstein, Henry L. Jaffee.

A COMMITTEE TO STUDY MEDICINE AND THE CHANGING ORDER has been organized by The New York Academy of Medicine. The objectives of this Committee are:

To be informed on the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and its services to the public may be preserved and embodied in whatever changed social order may ultimately develop.

The Committee plans to survey the changes that are currently taking place in our economic and social organization and to consider also any changes which are likely to take place during the next decade.

In this survey the Committee will solicit information and opinion from a wide variety of groups, including sociologists, economists, representatives of organized labor, industrialists, bankers and politicians.

Also, in this connection, the Committee will solicit the coöperation of those intimately connected with medicine in the capacities of deans of medical schools, teachers of medicine, hospital authorities, hospital clinicians, public health workers, those interested in graduate education, physicians in industrial medicine, medical social workers, and workers in voluntary health organizations.

We wish to emphasize the point that the Committee will devote itself primarily to the study of how, within the changing social order, the best qualities in medical service, in medical education and in medical research can be preserved and developed.

It is expected that the study will continue until sufficient evidence has been accumulated to make possible a considered report.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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1943

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



JULY, 1943

ROLE OF THE KIDNEY IN THE GENESIS OF HYPERTENSION*

HOMER W. SMITH, WM. GOLDRING AND HERBERT CHASIS

The Departments of Physiology and Medicine, New York University College of Medicine, New York City

position on this program is suggestive of the role of an intermediary between exploratory investigation and practical medicine. Whether or not it was the intention of the program committee, I am sandwiched between theory and practice and shall endeavor to discharge my responsibilities by discussing the evidence for and against the belief that the kidneys are primarily responsible for the genesis of essential hypertension.

For some years a group of investigators at New York University College of Medicine have been studying this question from the point of view of the renal circulation. William Goldring, Herbert Chasis and Hilmert Ranges are the investigators concerned, and I must emphasize to you that I appear here tonight merely in the capacity of a spokesman for my colleagues. Not only am I indebted to them with respect to published investigations, but at my request Goldring and Chasis have prepared for me the digest of literature which I shall later review. Needless to say, however, we are in complete agreement in respect to interpretation and I gladly assume the responsibility for what I have to say.

^{*} Read at the Stated Meeting of The New York Academy of Medicine, February 4, 1943

As a physiologist and a neutral observer of the pros and cons in the long-standing debate on the role of the kidney in hypertension. I have no subjective reasons for pulling my punches.

Last year we published a study of the effective renal blood flow in sixty subjects with essential hypertension, many of whom had been followed for a considerable period of time. We emphasized that the renal blood flow by itself is an unreliable datum since the quantity of functional renal parenchyma in various individuals, and especially in individuals with diseased kidneys, varies considerably. Consequently in that report the quantity of functional renal parenchyma present in each subject was evaluated by means of the saturation method and the effective blood flow was in each case referred to this primary datum. The resulting ratio of the effective blood flow per unit of residual functional tissue is remarkable for its constancy in normal subjects, and it constitutes an index to which considerable significance, in our opinion, may be attached in subjects with vascular or renal disease.

Omitting the finer technicalities of that study, we concluded that our evidence was against the belief that renal ischemia exists primary to the development of essential hypertension. It is true that renal ischemia is present in many hypertensive subjects, but this ischemia appears to be a result of the presence of vasoconstrictor substances in the blood, since it is readily reversible by agents which produce renal hyperemia in normal subjects, and during induced hyperemia the effective blood flow per unit of functional rental tissue is of the same order of magnitude in hypertensive subjects as in normals. The ischemic tendency is still present after renal denervation, which is why we think that it is of humoral origin.

It does not advance our problem, and it is of course illogical, to suppose at one moment that humoral agents are operating to reduce renal blood flow and then at the next moment to suppose that the reduction in renal blood flow is the reason for the appearance of these agents in the blood.

An even more cogent line of evidence is available in a second study made by Chasis and Redish² of the effective renal blood flow in the separate kidneys of twenty-one hypertensive patients. If it is predicated that renal ischemia is the primary causal factor underlying essential hypertension, the factors giving rise to this ischemia must be sought in anatomical faults which obstruct some greater or lesser fraction of the

renal circulation. By the laws of chance, and in accordance with the experience of pathologists, such obstructions would not be distributed symmetrically nor would they, except in rare instances, affect the renal blood flow symmetrically. Consequently, unilateral ischemia should be observed much more frequently than symmetrical bilateral ischemia. Yet among these twenty-one hypertensive patients the effective blood flow per unit of functional tissue was, within limits of variability no greater than are observed among normals, identical on the two sides. Not a single one showed unilateral impairment. This result is compatible only with the view that the ischemic tendency operates equally upon the two kidneys, and it is difficult to see how this could be the case if ischemia per se is the beginning of the story.

Proponents of the ischemic theory sometimes obscure the argument

Proponents of the ischemic theory sometimes obscure the argument by hypothesizing that in essential hypertension a multitude of microscopic Goldblatt clamps have been placed upon the finer renal arterioles. But this is a begging of the question. If we are to respect the meaning of words and the sequences of pathology, then those who would put clamps upon all or a large fraction of the renal arterioles must forthwith abandon the primacy of renal ischemia in the argument of causation, and accept the primacy of arteriolar disease of as yet unidentified origin.

To summarize these clinical studies, then, the renal ischemia which is present in some hypertensive subjects affects both kidneys equally; it is of a physiological, reversible nature except in very late stages, and under reversal a hyperemia as good as is enjoyed by normal kidneys results; it appears to be of humoral origin, since denervation does not abolish it. Faced with these facts we interpret the observed renal ischemia as one of the sequelae of the disease, and not its cause. The renal arterioles in man appear to be rather more sensitive normally to vaso-constrictor agents than they are in the dog, the only other well-studied species. It would be profitable, perhaps, to make in man a quantitative study of the relative sensitivity of the renal arterioles as compared with those of the skin and muscle mass.

From this point, then, let us reword our problem by asking what is the evidence that the kidneys play any part in the origin of hypertension? There comes to your mind immediately, no doubt, the Goldblatt experiment, and I would answer this apparently convincing argument by saying that this is only reasoning by analogy. I will reply by drawing an analogy. Had someone applied a clamp to the pancreatic

artery before the days of Minkowsky and obtained diabetes (and I have no doubt but what the judicious application of a clamp to the pancreatic artery would produce some form of diabetes or at least glycosuria), there would have come into existence the theory that diabetes was due to pancreatic ischemia. We know, of course, that that is not so and indeed it is probably the very rare case in which pancreatic ischemia plays any part. When Minkowsky took out the pancreas and obtained diabetes, there came into existence the theory that diabetes in the historic and literal sense of glycosuria, is due solely and simply to an underproduction of insulin. We now know that this is not true. The essential clinical signs and symptoms commonly identified as diabetes, i.e., decreased glucose tolerance and glycosuria, may be brought into existence by disturbances in the pituitary gland, in the liver, and possibly in the adrenal cortex, in animals and individuals in which the pancreas is not primarily at fault, whatever intermediary role the pancreas may play. What, then, are the causes of diabetes? They are multiple, and in no instance do we yet know the whole answer. The Goldblatt experiment shows that you can produce hypertension in the dog by renal ischemia. The experiment in principle is unquestionably applicable to man, but it proves nothing logically about the sequence of events in that large group of patients who have so-called "essential hypertension."

What other evidence is there to indict the kidneys? There come to mind numerous papers published in the last few years which, whatever their intent, give the impression of demonstrating that unilateral renal disease is causally related to a hypertensive process. The proof consists in the purported reduction of the hypertension by the removal of the offending kidney. There is, unfortunately, no criterion of the presence or intensity of hypertensive disease except the elevation of the blood pressure itself, or the subjective distress and eye-ground changes which are presumed to be sequelae of the elevated blood pressure; and blood pressure is an extraordinarily complex dynamic product of the circulation in which changes are difficult to interpret even under optimal conditions for the most precise study. I need not dwell upon the lability of the blood pressure in many hypertensive subjects, since this lability has been discovered by every investigator who has attempted to work under controlled conditions.

But because of the importance which this surgical-pathological literature assumes in the general impression, I have asked my colleagues

63

91

9

19

2

69

7

Per cent Cases 25 Papers 100 76 51 39 Negative results reported 49 37 Positive results reported Of these, 30 are incorrectly appraised because: 27 8 a. BP did not fall into normal range 1 3 b. Inadequate control ...

TABLE I UNILATERAL NEPHRECTOMY

Cases

c. Inadequate postoperative follow-up

Final appraisal: Negative results

d. BP returned to hypertensive level in 6 months

Positive results

to review it in toto and to appraise it critically under rigid but reasonable specifications.*

It is convenient to break this literature into several categories, the first of which consists of those papers, 25 in number,327 in many of which a reduction in blood pressure has been reputed to follow unilateral nephrectomy, the removal of the kidney being indicated by demonstrated or suspected unilateral renal disease (Table I). Seventysix cases are reported in these 25 papers, and in 51 per cent of these cases the authors themselves report negative results in respect to blood pressure reduction. Of the 49 per cent in which a positive result was obtained in the authors' opinion, 30 cases are held by my colleagues to be incorrectly appraised either because the blood pressure did not fall into the normal range, because there was an inadequate control study to establish true hypertension, because there was inadequate postoperative follow-up, or because the blood pressure was shown to return to hypertensive levels within six months. So in the final appraisal, out of the total of these 76 cases, unilateral nephrectomy has had a favorable result in respect to the reduction in blood pressure in 7 cases only.3, 7, 9, 14, 17, 18, 19 Accepting these 7 cases on their face value, in only one case in ten in which the thesis has been tested by nephrectomy is there evidence that the hypertensive process has its origin in disease of one kidney.

Table II

ALLEGED COMPRESSION OF THE RENAL ARTERY OR RENAL PARENCHYMA

| Obstruction of renal artery Renal compression | | 7 3 |
|---|--|------------------|
| | Total | 10 |
| Hypertension may have preceded plaque Questionable compression of renal artery by aortic aneurysm Bilateral renal disease not excluded Blood pressure did not fall after nephrectomy | | 1 1 2 2 |
| | Unsatisfactory | 6 |
| Apparently satisfactory | pparently satisfactory only 4 in entire literature | |

The second category deals with instances of hypertension supposedly arising from mechanical compression of the renal circulation or the renal parenchyma (Table II). There are a total of 10 cases in the literature. 6, 7, 15, 17, 27, 28, 29, 30, 31, 32 seven of which had obstruction of one sort or another of the renal artery, while 3 had renal compression. On reviewing these records, one must be discarded because there was a possibility that hypertension may have preceded the formation of the plaque which at necropsy was discovered in the renal artery; one was a suppositious compression of the renal artery by an aortic aneurysm, but being suppositious, is scarcely admissable as positive evidence. In two cases bilateral renal disease was not excluded, and in one of these it was quite definitely indicated. In two cases the blood pressure did not fall after nephrectomy, indicating that when put to the final test the assumed explanation failed to work. This leaves us with 4 cases only in the entire literature in which apparently satisfactory correlation is established between gross obstruction of the renal circulation and hypertension. We accept these 4 cases at their face value as demonstrating the applicability of the Goldblatt experiment to man, without generalizing beyond the limited evidence.

Turning now to the other aspects of the problem, we come to the third category of papers in which it is claimed that there is an abnormally high incidence of urologic disease in hypertensive subjects (Table III). Schroeder and Steele³³ have reported 113 urologic anomalies out

TABLE III INCIDENCE OF UROLOGIC DISEASE IN HYPERTENSION

Schroeder and Steele (1941) report 113/250 positives among living patients, or 45 per cent. Of these:

53 had bilateral renal disease:
8 had glomerulonephritis
17 had bilateral abnormal pyelogram
28 probable renal disease

Leaving 60/250 possible unilateral disease, or 24 per cent.

Wosika, Jung and Maher (1942) report 227/568 positives in necropsies, or 40 per cent, including all types of unilateral and bilateral disease, with no break-down.

of 250 living patients with hypertension, or a 45 per cent incidence of urologic fault. We exclude from this list 53 who had bilateral renal disease; 8 who had glomerulonephritis, 17 with bilaterally abnormal pyelograms, and 28 in whom renal disease was suspected but not proven. This leaves 60 patients with apparent urological fault out of 250 hypertensives, or 24 per cent. However, the judgment of urologic fault in this series was based largely upon abnormal radiograms obtained by intravenous or retrograde pyelography, and it has been our experience that the diagnosis of abnormality in a pyelogram is a very hazardous matter, since an innocuous angulation of the ureter or dilatation of the pelvis can give the visual impression of significant abnormality, although there is actually no obstruction of the lumen or evidence of renal impairment. The incidence of such apparent abnormalities in adults giving no history or evidence of abnormal renal function or of hypertension is very large. The significance of many of the residual 60 cases in Schroeder and Steele's series is therefore open to some doubt.

Wosika, Jung and Maher³⁴ have reported 227 urologic abnormalities out of 568 necropsies of hypertensive subjects, or an incidence of 40 per cent. These authors, however, include all types of unilateral and bilateral disease, and since they offer no break-down it is impossible to evaluate even the approximate significance of this figure with respect to the relation between unilateral diseases and hypertension.

The fourth category of paper deals with the incidence of hypertension in pyelonephritis (Table IV). In 500 cases of pyelonephritis, Pearman, Thompson and Allen³⁵ found that only 9 per cent had hyper-

TABLE IV
INCIDENCE OF HYPERTENSION IN

| Cases | | Per cent. with Hypertension |
|-------|---|--------------------------------|
| 500 | Pyelonephritis (unilateral & bilateral) | 9,0 |
| 500 | Goitre without hyperthyroidism | 100 |
| 500 | Gall-bladder disease . | 7 0 |

From Pearman, Thompson and Allens

TABLE V
INCIDENCE OF HYPERTENSION IN UROLOGIC DISEASE

| | | | Per cent with Hyperten.ion |
|------------|--|------|-------------------------------|
| 1. | Friedman, Moschkowitz and Marrus ¹⁵ | } | |
| | 193 unilateral renal disease proven at operation | | 21.8 |
| | 1006 living controls | } | 228 |
| 2. | Oppenheimer, Klemperer and Moschkowitz ²¹ | | |
| | 79 necropsied patients with unilateral renal disease | | 27,5 |
| | 333 control necropsies | i | 24 0 |
| 3 . | Baggenstoss and Barker ^{a6} | [| |
| | 97 necropsied patients with unilateral renal disease | | 29,3 |
| | 100 control necropsies . | | 29.0 |
| 4. | Braasch, Walters and Hammers | } | |
| | 1684 living patients with surgical uropathology | | 18.7 |
| | 975 living controls | ľ | 20.0 |
| 5. | Crabtree and Chaset ¹⁶ | | |
| _ | 150 nephrectomies for unilateral renal disease | ĺ | 9.0 |
| | (1981 living controls from 1 and 4) | 21.4 | |
| | (433 necropsy controls from 2 and 3) | 26.5 | |

tension, a figure that compares favorably with goitre without hyperthyroidism and with gall-bladder disease. This result is wholly incompatible with the belief that unilateral pyelonephritis tends to cause hypertension.

The last category of paper examines the incidence of hypertension in patients with demonstrated unilateral renal disease (Table V). Friedman, Moschkowitz and Marrus¹⁸ found an incidence of hypertension of 21.8 per cent in 193 patients with unilateral renal disease proven at operation. This figure is lower than the 22.8 per cent incidence which

these authors found in a control series of 1006 living patients. Again Oppenheimer, Klemperer and Moschkowitz²¹ found a 27.5 per cent incidence of hypertension in 79 necropsies where unilateral renal disease was demonstrated, a figure not significantly above the 24 per cent of hypertension which they found in 333 control necropsies. Baggenstoss and Barker³⁶ similarly found an identical incidence of hypertension in patients with and without unilateral renal disease, while Braasch, Walters and Hammer³⁷ found 18.7 per cent incidence of hypertension in 1684 living patients with surgical uropathology, a figure slightly less than in their 975 living controls. Lastly, Crabtree and Chaset¹⁶ found only 9 per cent incidence of hypertension in 150 patients who had suffered nephrectomy for unilateral disease. Combining the living controls in 1 and 4 (Table V) the incidence of hypertension should have been 21.4 per cent, or considering the necropsy controls in 2 and 3, the incidence should have been 26.5 per cent. These figures are of the order of magnitude accepted by most medical statisticians as designating the incidence of hypertension in the adult population. Obviously, in Crabtree and Chaset's 150 patients, unilateral renal disease had exerted a very favorable influence on the frequency of high blood pressure!

The data summarized in this Table are impressive in their statistical demonstration that unilateral renal disease and surgical uropathology do not predispose to hypertension. Add to them the data from Pearman, Thompson and Allen in Table IV, with 9 per cent hypertension in 500 pyelonephritics, and the argument for renal origin appears tenuous indeed. The positive evidence on critical review boils down to seven cases in whom unilateral nephrectomy apparently effected a reduction in blood pressure and four cases in which a gross obstruction or compression of the renal circulation could have accounted for the hypertensive process, and we have in the recorded literature eleven cases in favor of the argument.

We conclude, therefore, that unilateral renal disease is rarely a cause of hypertension in man.

But how about bilateral renal disease? You will recall that it was Richard Bright^{38,39} who first associated the elevation of blood pressure with kidney disease. He was impressed by the left ventricular hypertrophy of nephritis and allied diseases, and even in the absence of methods for measuring blood pressure, he deduced that there must be an increased load thrown upon the heart, and inferred that this load was

due to the resistance offered to blood flow by the kidneys. Later Johnson⁴⁰ and after him Gull and Sutton⁴¹ demonstrated that in hypertension arterioles in other organs in the body were frequently narrowed as well, and then Allbutt⁴² and Huchard⁴³ demonstrated that hypertension could exist in the absence of sclerosis of either the renal or systemic arterioles. From this observation, frequently confirmed, arose the conception that hypertension could exist in the absence of renal or systemic arteriolosclerosis, and consequently the aggregation of diseases formerly called "Bright's disease" was divided into those in which the kidneys were primarily involved, i.e., glomerulonephritis, polycystic renal disease and pyelonephritis, and those in which the kidneys were involved only secondarily to the hypertension. Hence the latter came to be called "essential hypertension." It seems to us that this division is still warranted.

But why does the blood pressure rise in glomerulonephritis, bilateral polycystic renal disease and bilateral pyelonephritis, if the kidneys are not primarily responsible for the pathological process in the large majority of patients with essential hypertension? The answer to this question can be identical with the answer which we have opposed to generalizing from the Goldblatt experiment: the kidneys can be the cause of elevated blood pressure where both organs are initially diseased, and in rare cases where only one kidney is affected, though whether the significant perturbation here is renal ischemia or some breakdown in renal metabolic activity cannot as yet be said; but the acceptance of this fact must not lead us into accepting the rare explanation for the general rule. The statistics are against it: hypertension has no higher incidence with unilateral renal disease than in the general population, and in the unilateral nephrectomies so far reported, in the opinion of the authors 50 per cent are improved, by our accounting only 10 per cent. In the nature of the problem, the true improvement is probably less.

It seems to us, therefore, that under the surgical and pathological evidence, as under the physiological evidence, the theory of primary renal origin is unproved. So far as the genesis of essential hypertension is concerned, the kidney appears to be the victim rather than the culprit. This is not to argue, however, that if the genesis is complex the kidney may not play an intermediary role, even as the pancreas may play a role in all perturbations of carbohydrate metabolism. But to ven-

ture in this direction is pure speculation. At this moment the origin of essential hypertension is unknown.

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SPECIAL ASPECTS OF THE PROBLEM OF THE RENAL ORIGIN OF HYPERTENSION*

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facility in animals by constriction of the renal arteries or compression of the renal parenchyma, the question has become pertinent whether essential hypertension in man also has its origin in the kidneys. It is obvious that gross obstruction to the renal blood flow and pressure on the parenchyma occur but rarely in human beings. But is gross obstruction or pressure necessary? If this is so, it is doubtful that the kidneys are responsible for most human hypertension, or that experimental renal hypertension has wide significance in clinical medicine.

The term "ischemia" of the kidneys has been so extensively employed that it has almost become synonymous with the term, "renal hypertension." Indeed, so little regard has been given to its definition, that one group of authors state: "By the term renal ischemia, we imply those changes which occur in the kidney following constriction of the renal artery with a Goldblatt clamp, be it actually ischemic, diminished pulse pressure, change in pulsatile flow or other factors." Clearly the term is well on the road to becoming meaningless. This is not necessary as the dictionary definition is clear: "local anemia due to mechanical obstruction to the blood supply."

It is the province of this communication to examine the evidence concerning three related problems: (a) whether experimental renal hypertension, human essential hypertension and hypertension induced by angiotonin are similar and hence study of one will lead to elucidation of the others; (b) whether "ischemia" in the sense of anemia of the renal tissue is the factor initiating and maintaining hypertension in experimental and human hypertension; (e) whether the so-called, "amine intoxication" theory of hypertension is consonant with the clinical and hemodynamic picture of experimental and human hypertension.

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Similarities of Experimental Nephrogenic Hypertension, Hypertension Elicited by Angiotonin and Human Essential and Malignant Hypertension

Justification for the great interest in experimental nephrogenic hypertension must ultimately come from the demonstration that it mimics essential and malignant hypertension in man. That a similarity exists has been apparent for some time, especially when due allowance was made for the anatomical and physiological differences between quadrupeds and man. This is perhaps most strikingly illustrated by the differences in psychic and somatic expressions of the nervous system during the disease. The aggressiveness and emotional instability of the typical human hypertensive are well known, but it is important to realize that the full blown disease may occur in their absence. Somatic expressions of hyperactivity of the nervous system usually consist of blushing, tachycardia, sweating, tenseness, etc., but these may or may not be present. It should cause no surprise that these varied manifestations are not found in hypertensive dogs, rabbits or rats. Furthermore, since these animals are quadrupeds the reduction in blood pressure which very often accompanies extensive sympathectomy in man is not seen. According to a view of Corcoran and Page¹ the benefits of sympathectomy do not depend on improvement of renal circulation but rather in part on denervation of the human reactive visceral splanchnic area, with resultant partial failure of venous return, most evident in the erect posture. Since dogs seldom stand erect, it is understandable that fall in blood pressure due to this mechanism would not occur in them. In addition, there is a vast difference in organization of canine and human nervous systems and this, too, must play some part in the results of sympathectomy. In some cases of human hypertension there is reason to suspect that the nervous system participates more actively than in others. In short, this is an example of the differences in signs and symptoms which might be anticipated from knowledge of the substrate on which the disease acts and from our beliefs as to its origin.

Despite these, in most cases, small differences, the similarities are great as will be clear from perusal of Table I. To my mind the most striking observation is that the hemodynamic picture is almost identical in both human beings and dogs and even the effects of the disease on the organism has some similarity.

TABLE I

COMPARISON OF EXPERIMENTAL RENAL HYPERTENSION, HUMAN ESSENTIAL HYPERTENSION AND HYPERTENSION INDUCED BY ANGIOTONIN

| Experimental Hypertension. | Human Essential Hypertension | Angiotonin Hypertension |
|--|---|--|
| Heart | | |
| Hypertrophy, left ventricular Force—Increased Work Efficiency—increased Output—normal or reduced Coronary sclerosis—not found Rate—normal Pulmonary arterial pressure—normal | Same Increased Increased Normal or reduced Common Normal Normal | Increased Increased Normal or reduced Not known Normal or slowed Increased in acute experiments |
| Venous pressure—normal | Normal | Often elevated in acute experiments |
| Kidneys | | acare experiments |
| Thickening of arteries—common Early morphological changes—none Maximal ability to concentrate—reduced | Common None | Not known Not known |
| early Glomerular filtration—maintained Blood flow—normal or reduced | Reduced early Maintained Normal or reduced | Not known Maintained Reduced in acute |
| Filtration fraction—elevated Diodrast Tm—slowly reduced Renin secretion—increased Unilateral renal disease—sometimes | Elevated Slowly reduced Increased | experiments Elevated Slightly reduced |
| cured by nephrectomy | Same | |
| Liver | | |
| æ globulin production-increased | Increased | Not known |
| Arteriolar constriction, present Arteriolar sclerosis, present Hemorrhages, exudates present Papilledema, present Retinal detachment, present lentral Nervous System | Present Present Present Present Present | Present Not known Not known Not known Not known |
| No evident change | Many somatic expressions of | None |
| Sympathectomy—no change in blood pressure Adrenalectomy—reduces arterial pressure Hypophysectomy—reduces arterial pressure moderately Thyroidectomy—no effect on pressure Pancreatectomy—no effect on pressure Gonadectomy—no effect on pressure | hyperactivity in some patients. Need be none. May reduce blood pressure Probably reduces pressure Possibly reduces pressure No effect Not known No effect | Does not affect response Reduces response only terminally No marked reduc- tion in respon- siveness No effect on responsiveness No effect on |

Added to this is the fact that angiotonin, when injected into either animals or man, reproduces these hemodynamic changes with a reasonable degree of fidelity. Especially remarkable is the observation that it raises blood pressure asymptomatically and by narrowing the peripheral arterioles and increasing the force of the heartbeat the arterial pressure is raised, yet peripheral blood flow is not reduced. This is an unusual feat among the known pressor agents.

The evidence thus points clearly to the assumption that experimental renal and human hypertensives have much in common. Subsequent developments have suggested strongly that angiotonin has properties which are consonant with those which might be expected of a substance causing both experimental and human hypertension. The evidence is certainly not complete but enough has been accumulated to make me feel that it is angiotonin of renal origin, or something very similar to it, that mediates hypertension.

Is "Ischemia" of the Kidneys the Factor Initiating Hypertension?

It is understandable that following the demonstration of hypertension resulting from compression of the renal arteries, the assumption was made that it was a result of renal ischemia and reduced oxygen tension. The term, "ischemia," has been subsequently widely used and accepted as though proven by adequate evidence.² Indeed, some evidence supports this view, especially that demonstrating ischemic atrophy of the kidneys following clamping of the arteries (Goldblatt²) and reduction of blood flow distal to the clamp in the renal artery (Levy, Light and Blalock³). Goldblatt states that: "the changes in the tissues of animals with persistent hypertension and without signs of uremia were therefore abiotrophic rather than necrobiotic." "It is to those abiotrophic changes in the kidneys that the elevation of blood pressure is probably attributable because it is well known that in acute experiments clamping even of both renal vessels has little or no immediate effect on blood pressure."

Despite wide acceptance, the evidence supporting this view seems inadequate. Indeed, if ischemia of any significant degree were necessary for the production of hypertension, the methods now employed to elicit experimental hypertension would have little in common with the naturally occurring essential hypertension, for in the latter, evidence

of ischemia at times occurs only late in the disease. During the course of studies in dogs in which clamps were applied to the renal arteries or silk perinephritis induced, Corcoran and I⁴ were early impressed by the fact that hypertension of marked degree resulted in animals in which there were no macroscopic or microscopic changes in the kidney tissue characteristic of ischemia. The problem, then, was not whether ischemia with hypertension could be produced by sufficient compression of the renal artery or parenchyma, but whether compression of a grade insufficient to produce ischemia resulted in hypertension.

Clearance methods were the most practical ones for measuring blood flow in the explanted kidneys of our dogs. In the initial phase of the work (Corcoran and Page^{4,5}) creatinine clearances were used as a measure of glomerular filtration and phenol red of renal plasma flow. It was shown that hypertension could be produced by clamping the renal artery without more than transient alterations in these clearances which suggested that neither renal blood flow nor intraglomerular pressure was decreased. Similar results have been obtained by Alpert and Thomas.⁶ Later, inulin clearance (C1) was used to measure glomerular filtration, and diodrast clearance (CD) the effective tubular blood flow. The maximal ability of the tubules to secrete iodine from diodrast offered to them was used as a measure of the total amount of functioning tubular tissue, the so-called effective tubular mass or, briefly, Tm_D. The term, "tubular mass," refers to the amount of tubular cells which is able to secrete diodrast.

Using these more accurate methods, renal blood flow and relative intraglomerular pressure were again found normal in many dogs with hypertension induced by perinephritis or clamping the renal artery. Confirmation of these findings is found in the experiments of Friedman, Sugarman and Selzer in which renal blood flow was not reduced when hypertension followed constriction of the aorta just above the mouths of the renal arteries.

Determination of diodrast clearance (CD) in man with early hypertension shows that it often is reduced but may be normal, and the same is true of tubular mass (Tm_D). Thus the ratio CD/Tm_D in most hypertensives will express the reduction in blood flow per unit of tubular mass; in short, ischemia of the tubules. The question remains to explain why some early hypertensives exhibit tubular ischemia and some do not. Blood flow in the kidney will depend at least on two opposing

forces, the resistance within the kidney itself and the mean systemic arterial pressure.⁸ Most contemporary evidence (Corcoran and Page') (Friedman, Selzer and Rosenblum⁹) suggests that resistance within the kidney early in hypertension is due in large measure to vasoconstriction produced by humoral agents. These agents elicit vasoconstriction of a very special kind, namely, constriction of the afferent and efferent glomerular arterioles, the small muscular arterioles just proximal and distal to the glomerular capillary tufts.

Constriction of the afferent arterioles will tend to damp the effects of the elevated systemic pressure and reduce intraglomerular pressure, whereas constriction of the efferent arterioles will tend to elevate intraglomerular pressure. The latter will be reflected in the filtration fraction from inulin clearance. Peritubular blood flow will tend to be reduced by the constriction of both and this will be reflected in reduction of diodrast clearance. Lamport¹⁰ has recently presented a very interesting mathematical formulation of this viewpoint which aids in clarifying the many complex factors involved.

Actually in hypertensives the inulin clearance is slightly reduced or is normal. The cause of this slight reduction in filtration is not certainly known. It is probable that it results from some measure of constriction and possibly obstruction in the afferent vessels.

When the amount of glomerular filtration is considered in its relationship to tubular mass a different picture appears. Now its relative value per unit of functional tubular tissue (CI/TmD) exceeds the mean normal value. In short, a relatively high filtration rate is being maintained in the kidneys of hypertensives, due, apparently, to increased systemic pressure and to efferent arteriolar constriction.

If resistance to blood flow in the kidneys increases, the systemic pressure may rise to oppose it and the actual blood flowing through them will be a balance struck between these forces. In short, as Corcoran and Page⁸ found, the relative level of effective renal blood flow in hypertension is directly proportional to increased arterial pressure and inversely proportional to increased vascular resistance. It is not surprising, therefore, that the observed blood flow may be normal in some hypertensives and reduced in others. It follows that the finding of a normal rate of renal blood flow or a normal relationship between tubular mass and the blood flowing to it cannot be used as evidence against the participation of the kidneys in the genesis of hypertension.

As stated, the increased resistance within the kidneys seems to be mediated by substances in the blood. At present there is no certainty what these substances are but good evidence suggests the participation of angiotonin. The demonstration (Corcoran, Kohlstaedt and Page¹¹) that angiotonin reproduces the intrarenal hemodynamic changes characteristic of hypertension adds weight to this belief, but does not prove it because a few other substances exhibit similar properties. As an isolated argument, the renal action of angiotonin can only place it among several substances which might be genetic factors in the development of hypertension.

While the evidence supporting the interpretation of clearance measurements is rapidly becoming stronger, there are reservations which must be clearly recognized. One of the most important of these is that reduction in diodrast clearance (CD) may result from decreased effective renal blood flow or decreased extraction ratio, i.e., the ability of the rubular cells to extract diodrast presented to the cells by the blood, and at present there are no data to distinguish between these alternative explanations. There is no compelling evidence of decreased overall extraction of diodrast in the hypertensive's kidney. If, then, it is assumed that all of the diodrast is removed from the blood by the tubules as it is presented to them, then the diodrast clearance measures blood flow to the tubular tissue. The blood flowing to non-secreting tissue is not measured by this clearance; and hence, the relationship between total renal blood flow and flow to functional tubular tissue, in disease especially, is uncertain. Clearly, interpretation of the results of these methods must be made with the same care as Smith12 and others have done. Nevertheless, they are the only ones capable, for instance, of determining the effectiveness of tubular cells damaged by scars, blockage and the other vicissitudes of disease.

In this connection, it may be pointed out that Goldring, Chasis, Ranges and Smith¹³ are inclined to interpret the apparent lack of tubular ischemia in some hypertensives to the appearance in the kidneys of so-called "impotent nephrons." By impotent nephron they mean one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct despite the fact that it has lost its secretory activity, as tested by diodrast. Whether such impotent tubules lose all other tubular properties, such as capacity to reabsorb glucose, has not as yet been determined. Since by definition, impotent

nephrons are unable to secrete diodrast they do not contribute to diodrast clearance (CD) or tubular mass (TmD). The increased volume of blood per unit TmD which is made available for clearance by formation of impotent nephrons will appear in clearance measurements as apparent hyperemia of the residual functional tissue. Unlike the true hyperemia resulting from either dilatation of the renal arterioles or increased perfusion pressure, the blood may be deficient in some of its vital supportive qualities. Demonstration of the existence of impotent nephrons and of the inadequacy of blood from them to support normal tubular cells may prove to be an important aspect of renal physiology.

It is conceivable that reduced blood flow could occur to some tubules and not to others; a "patchy ischemia." But since there is no histological or other evidence of this and since it is not a necessary argument to describe the mechanism of the liberation of renin, proof of the existence of focal ischemia must await further observations.

We are now in a position to consider other evidence relating to the problem of intrarenal blood flow and pressure and its association with hypertension. Levy, Light and Blalock³ found a decrease in blood pressure in the renal artery distal to the clamp, as well as decreased blood flow per gram of renal tissue when hypertension was present, suggesting that ischemia was necessary to the occurrence of hypertension. Despite decreased blood flow no anoxia could be demonstrated by determination of arterio-venous difference (Mason, Evers and Blalock¹⁴). Dock and Rytand¹⁵ found the rate of flow of blood per gram of kidney tissue normal in rats with hypertension produced by subtotal nephrectomy. They indicate clearly that these hypertensive rats did not have renal ischemia.

Later experiments of Mason, Robinson and Blalock¹⁶ show that the blood pressure distal to the clamp may return to normal, yet the hypertension persist. The pulse pressure, however, remains depressed.

The oxygen consumption of ischemic rabbits' kidneys was found to be reduced by Gerbi, Rubenstein and Goldblatt.¹⁷ In general the degree of degeneration of the renal parenchyma was a fairly good indicator of the probable value of Qo₂, the lowest values corresponding to the most damaged kidneys. But diminution of tissue respiration occurred in some of their experiments without any histological changes. Mason, Robinson and Blalock,¹⁶ on the contrary, found no change in respiratory activity in so far as this is indicated by the respiratory quotient and the

degree of aerobic glycolysis in kidneys of either hypertensive dogs or rabbits.

It is difficult to explain these completely discordant observations. Mason, Robinson and Blalock write that they repeated their experiments after the appearance of the paper by Gerbi, Rubenstein and Goldblatt, finding the results as before.

If low oxygen tension in the kidneys were part of the mechanism of renal hypertension, it might be anticipated that administration of high concentrations of oxygen would reduce the elevated blood pressure. Steiner, Weeks and Barach¹⁸ have given pure oxygen to dogs with renal hypertension for 24 to 48 hours without observing any fall. Likewise three hypertensive patients did not respond with lowered blood pressure when they received the same treatment for three days. It is highly probable that any marked anoxia would be overcome by this treatment and if anoxia were part of the mechanism of hypertension, its abolition should reduce arterial pressure. Approached the other way, it might be anticipated that when the oxygen saturation of the blood is greatly reduced as often occurs clinically, arterial pressure should rise. It rarely does. Such experiments, of course, do not answer the question whether change in blood distribution within the kidneys themselves might not produce focal hypoxia.

Evidence of a different kind has been furnished by Kimmelstiel¹⁹ and by Cox and Dock.²⁰ They estimated the capacity of the vascular bed of kidneys by perfusion after death, finding that in kidneys of most patients with hypertension but without uremia, it was within normal range. Blackman,²¹ on the other hand, concluded from study of fixed tissues that narrowing of the renal arteries was usual. Cox and Dock consider his results erroneous and due merely to rigor and to the tissue fixation.

Several investigators (Fishberg;²² Bell and Clawson;²³ and Williams and Harrison²⁴) have observed many patients with hypertension in whom the changes in the renal vessels were of such slight degree as to furnish no adequate explanation for the genesis of the increased arterial pressure. Smithwick²⁵ has observed insignificant vascular changes in the vessels of biopsy specimens taken from the kidney during sympathectomy.

This evidence taken as a whole offers little support for the view that persistent reduction in blood flow and oxygen utilization occurs within the kidneys except when hypertension is of long duration and severe

secondary vascular change has supervened. For these reasons it seems doubtful if the oxygen tension within the kidney is reduced sufficiently early in hypertension to initiate some of the reactions leading to the formation of substances such as hydroxytyramine by anaerobic decarboxylation except late in the course of the disease. In the past year an array of theoretical papers have appeared in which the assumption is accepted as though it were a fact that hypertension is due to anoxia and ischemia of the kidneys.

What then are some of the factors which might initiate the liberation of humoral agents responsible for hypertension? Unfortunately, this problem has not been intensively studied. Kohlstaedt and Page²⁶ found in artificially perfused kidneys that reduction of blood flow without simultaneous reduction in pressure did not lead to liberation of renin but reduction of pulse pressure was shortly followed by its appearance in the renal vein. From these results it was suggested that reduction of pulse pressure is the initiating factor causing liberation of renin. What causes reduced pulse pressure we do not know, nor do we know why reduction in pulse pressure has this effect. Furthermore, artificial conditions had to be set up to perform such experiments. The changes in tissues occurring when the character of the pulsation is altered are known to be marked, but their precise nature is not known.

Amine Intoxication as a Cause of Hypertension

Various pressor amines have, from time to time, been suspected of causing essential hypertension but these suggestions never have been followed actively to ascertain the truth or falsity of the claim. For example, in 1935, Wolf and Heinsen²⁷ believed they had by crude methods demonstrated tyramine which originated in the kidneys in the blood of hypertensives. Paunz²⁸ found that long-continued infusion of tyramine caused morbid changes in the kidneys suggestive of nephrosclerosis. More recently, however, Enger and Lampas²⁹ were unable to find either hypertension or significant renal lesions in dogs given daily subcutaneous and intramuscular injections of tyramine (up to 300 mg.) for two and one-half years. Heinsen³⁰ investigated the question of the synthesis of tyramine by decarboxylation of tyrosine and concluded that pancreas alone could do this while spleen, kidney, liver, lung and muscle were unable to do so. Others found that tyramine was produced by the kidneys but Heinsen³⁰ after reinvestigation was still unable to

find it. Such studies as these carried little conviction.

But in 1937, Holtz³¹ announced that kidney pulp could convert tyrosine into tyramine by decarboxylation. Later³² it was shown that much more tyramine was found (or some pressor substance similar to it), if the reaction was allowed to progress under anaerobic conditions. In the presence of oxygen, amine-oxidases deaminized it to vaso-inactive aldehydes. This work has been the starting point for extensive investigations seeking to show that it is this or some similar mechanism which is responsible in whole or in part for hypertension.

Bing and Zucker³³ made the interesting observation that injection of dopa (1-dihydroxyphenylalanine) into the substance of a completely ischemic kidney converts part of it in two to four hours to a pressor substance with some of the properties of hydroxytyramine. Further, if dopa is injected into kidneys made partially ischemic by a Goldblatt clamp, a rise in blood pressure occurs. On the contrary, none occurs when the kidneys are normally perfused. No pressor substance is found, when dopa is perfused through liver or gut. It was then found³⁴ that under anaerobic conditions ground guinea pig kidney forms hydroxytyramine actively, but if oxygen is admitted, its production is quickly reduced by one-half or more. Extracts of guinea pig, cat and human kidneys all produce pressor substance under anaerobic conditions.³⁵

About the same time a series of articles appeared on the use of tyrosinase (a phenolic oxidase) in the treatment of experimental and human hypertension. The assumption was made that hypertension was due to the occurrence of mono- and dihydroxyphenolic amines such as hydroxytyramine and that tyrosinase or phenol oxidases would convert these to vaso-inactive quinones. Schroeder and Cohn³⁶ found that intravenous injection of tyrosinase consistently lowered blood pressure in hypertensive rats and dogs, but not in normal ones. This was confirmed in later work³⁷ and was extended to include human beings.³⁸ Schroeder has used mushrooms as the starting point for the preparation of his tyrosinase. Lately he writes39 that an amine-oxidase prepared from hog liver is also very effective in lowering blood pressure in hypertensive dogs and rats. The inactivated enzyme did not affect the blood pressure, but this is denied by Prinzmetal, Alles, Margoles, Kayland and Davis. 40 Such evidence as this, if substantiated, would be strong evidence in favor of the amine theory of the pathogenesis of hypertension.

Other groups of workers at the Mt. Sinai Hospital have actively

concerned themselves with this problem. Soloway and Oster⁴¹⁻⁴³ showed that various aromatic amines are destroyed *in vitro* by aeration in the presence of quinones. They assume that the ischemic kidney is deficient in oxygen, hence its ability to destroy amines is deficient. This deficiency can be overcome by supplying an additional hydrogen acceptor. Hence, they injected intramuscularly o-cresol indophenol, a hydrogen acceptor and found a fall of 30 to 40 mm. Hg in arterial pressure of hypertensive rats but none in normal animals. Working on the theory that pressor amines could be inactivated by the ortho-quinoid intermediaries formed during the course of tyrosinase action, Friedman, Soloway, Marrus and Oppenheimer⁴⁴ treated hypertensive rats with a number of quinones. Four of them were found to lower blood pressure effectively with only slight local reactions and no thermal reactions. Some of the preparations were effective by mouth. Again the arterial pressure of normal rats was not affected.

Supporting evidence that both in animals and human beings with hypertension, defective renal deaminization may be present due to renal ischemia is presented by Oster and Sorkin.45 In a series of five early hypertensives, intravenous injection of dopa produced a greater rise in arterial pressure than in five normotensives. The same procedure in hypertensive cats elevated blood pressure but not in normal ones or ones with acute renal ischemia. This is an extremely interesting observation and of sufficient importance to require very critical evaluation. Several obvious suggestions occur to mind: (1) the side effects such as nausea, vomiting, etc. which occurred frequently might well upset the results; (2) the early hypertensive has an especially labile blood pressure and hence the need for very exact control; (3) during the early phase of hypertension renal ischemia of any marked degree is unlikely to occur and since no measurements are given, the occurrence of "renal ischemia" remains conjectural; (4) only one reading of blood pressure is given before and one after injection of dopa; (5) the series is very small for the wide variation in the results. These suggestions are not given to disparage this work but point out that if the correctness of the work can be established, it would furnish a link in the evidence of genuine importance.

Evidence was found by Martin, Ichniowski, Wisansky and Ansbacher⁴⁶ that the oxidative destruction of adrenalin *in vitro* is promoted in a tyrosinase-adrenalin system by ortho-substituted phenols such as

catechol. Hence they administered tyrosinase along with catechol to a hypertensive dog and believed that the hypotensive effect was enhanced. This experiment had interesting possibilities but only one experiment is mentioned and the protocols of this not given, whether thanks to the authors or thanks to the editor.

It would certainly be premature at this time to attempt strict evaluation of the published results in this field. Many factors must be further investigated before a basis for sound judgment can be had. Already certain difficulties have appeared in the theory which may be hard to answer.

Amine-oxidase is absent from rats' kidneys^{47, 48} as determined by studies of tissue respiration. This has been confirmed by a histochemical technique.⁴⁹ Decarboxylase is also lacking. Despite these facts, hypertension is easily elicited in rats by the usual methods. Certainly, then, the amine intoxication theory does not apply to all animals. It is especially to be regretted that the very animal on which most of the work has been done does not appear to have either amine-oxidase or decarboxylase in the kidneys.

According to Alles, Blohm and Saunders⁵⁰ the tissues of mammals do not normally contain any considerable amounts of tyrosinase or other phenol oxidases. The inactivation of phenolic amines is largely carried out by an esterifying process. They find the dissociation constants and the oxidation rates of tyrosinase-amine combinations such that this mechanism cannot account for any considerable part of the inactivation of tyramine of adrenalin in normal animals. According to them, it seems doubtful that the therapeutic effects of tyrosinase are due to its action as a phenol oxidase.

The evidence submitted by Brown and Maegraith shows⁵¹ that the rate of oxidation by liver slices of tyramine is not reduced in hypertension experimentally produced. Tyramine evidently does not accumulate merely by not being destroyed.

There are certain other observations which must be considered in connection with the amine intoxication theory. Especially important among these is the type of vasoconstriction observed after administration of most pressor amines (Abell and Page⁵²). The type characteristic of the hypertensive is one in which the peripheral arterioles are chiefly constricted with sufficient fall in the gradient of blood pressure that capillary pressure is normal. Further, blood flow is not appreciably

reduced. Compare this with the type of vasoconstriction which occurs when most vasopressor drugs are injected. For instance, Landis, Montgomery and Sparkman⁵³ found adrenalin, tyramine, pituitrin, guanidine, methyl guanidine, etc. elevate arterial pressure but always decrease skin temperature with varying degrees of vasoconstriction. In a word, there is disproportionate increase of peripheral resistance with decrease of blood flow, a circumstance which does *not* occur in the hypertensive.

A second point of importance is that most pressor amines increase cardiac output greatly. Yet the output in hypertensives is either normal or reduced. Taylor and Page⁵⁴ point out that tyramine increases stroke volume and greatly reduces heart rate, resulting in slight reduction in cardiac output, while angiotonin decreases stroke volume without much reduction of rate resulting in marked reduction of cardiac output. This is not the place for an extended discussion of the cardiodynamic effects of various pressor substances. Suffice it to say that the effects of tyramine and most other amines are such as to make it unlikely that they participate in the genesis of renal hypertension.

Most pressor amines when injected into human beings cause symptoms and signs of a most disagreeable nature. Nausea, vomiting, sense of oppression, sweating, tachycardia or bradycardia, prolonged headaches, increased peristalsis of the intestine, increased metabolic rate, shortened circulation and mydriasis are usual. These are signs and symptoms seldom seen in patients with essential hypertension or dogs with experimental hypertension. However, they do occur in cases of hypertension due to liberation of the pressor amine, adrenalin, in cases of pheochromocytoma of the adrenal glands.

Whether anaerobiosis is sufficiently intense in the kidneys of hypertensives to initiate the decarboxylating mechanism seems doubtful. Most evidence gathered so far is against the view that it is. Possibly late in the disease when renal blood flow is seriously compromised, sufficient hypoxia may exist. Thus, in summary, it may be said that the theory of amine intoxication has some interesting experimental work substantiating it but also many important objections to it.

SUMMARY

The evidence concerning the following three questions has been examined: (1) Whether experimental renal hypertension, human essential hypertension and hypertension induced by angiotonin are similar

and hence study of one will lead to elucidation of the others? It was concluded that allowing for differences in organization of quadruped and man, the similarities especially as regards hemodynamics are great.

(2) Whether "ischemia" in the sense of anemia of the renal tissue is the factor initiating and maintaining hypertension? It was concluded that it was not a necessary factor and that the wide use of the term is unjustified by the evidence. (3) Whether the so-called, "amine intoxication" theory of hypertension is consonant with the clinical and hemodynamic picture of experimental and human hypertension. It was concluded that while interesting and important evidence has been presented, there are many serious difficulties that have not been explained which, on the whole, militate against its playing an important part at least early in the course of the disease.

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THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE*

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Introduction

Here, as in all fields of medicine, we are bound by fixed ideas as to underlying pathological processes and what is perhaps more serious by set patterns of therapy. Despite the fact that well known and reliable investigators still disagree as to the processes which produce atheromatous changes in the arteries, most of us have formulated a picture of these changes that is all too final in our minds and having formulated such an opinion we are wont to treat the patient with obliterating arteriosclerosis with a routine much too fixed to be effectual in every case. Too frequently the diagnostic terms themselves immediately center our therapeutic tendencies on an ineffectual method. As only certain cases of pulmonary tuberculosis should receive pneumothoraxonly certain patients with phlebitis may need chemotherapy or anticoagulants. It therefore behooves us to evaluate the organic changes present in any one condition and likewise determine what associated functional disturbance should be treated. Every woman whose hands and feet show vasomotor changes is not suffering from a Raynaud's syndrome. I shall therefore this afternoon devote my discussion to general pathologic processes involving the peripheral vascular system and their management. In order to conform to present day concepts of disease we must use names to describe the various processes encountered, but I hope to impress on your minds that a name so commonly used as arteriosclerosis actually covers a great variety of processes in the arteries, only a very small percentage ever leading to gangrene or amputation.

^{*} From the Department of Medicine, New York Post-Graduate Hospital and Medical School, Columbia University. Lecture given as part of a Refresher Course in Cardiovascular Diseases under the joint auspices of The New York Academy of Medicine and the New York Heart Association, March 24th, 1943.

CHART I
PROCESSES REDUCING ARTERIAL SUPPLY
WITH ASSOCIATED SYMPTOMS

| Process | Rate of Development | Symptoms and Signs |
|--|------------------------------|--|
| 1. Functional a. Complete Spasm | Sudden | Coldness, numbness, pain, pallor, gangrene |
| b. Recurrent Spasm | Gradual or varying in degree | Pallor, cyanosis alternating with rubor, coldness, super- ficial ulcerations |
| 2. Organic a. Embolism | Sudden | Coldness, numbness, pain, gangrene |
| b. Thrombosis Sclerosis Medial or Intimal | Gradual | Intermittent claudication, coldness, rest-pain, ulceration, gangrene |
| Thrombo- angiitis obliterans | Rapid | Same as with embolism. |

Note: Most organic occlusive processes are associated with functional disturbances

ARTERIAL DISEASES

When pathological processes involve the arteries and arterioles we have as a result alterations in blood supply to the part of the body supplied by these vessels. As a result of this alteration in supply the patient comes to us with certain symptoms.

If the supply is increased above the average, as it rarely is, we have a feeling of swelling, increased warmth and various paresthesias especially burning and throbbing. Erythromelalgia is about our only example of such a disease and is a rare condition. Since Weir Mitchell¹ described it as a neurological problem, no effective therapy has been found to relieve its distressing symptoms. One would expect that drugs working through the autonomic nervous system to produce arterial spasm would be therapeutically useful, but the annoying and serious side effects of such therapy have eliminated their value. If the supply is decreased we find a great variety of symptoms depending on many variable factors (Chart I).

It is therefore evident that there are many variables present in con-

CHART II

EVALUATION OF THE PROCESSES REDUCING ARTERIAL SUPPLY

- 1. Degree of spasm in the main and collateral vessels.
- 2 Rapidity of development of the process.
- 3. Type of process as it manifests itself in the wall of the vessel (Rule out blood dyscrasias).
- 4. Extent of involvement of the process: Locally and generally.
- 5. Association with other processes, such as phlebitis.

ditions which reduce blood flow through the arterial tree to an extremity. In addition to those enumerated in Chart I, one must consider the effect of alterations in cardiac output, as many individuals suffering from peripheral vascular disease also have associated heart disease. A failing heart will often allow sudden and serious arterial thrombosis to occur in peripheral arteries whose walls are already damaged. Before instituting treatment sufficient time must be spent to evaluate in each patient with reduced arterial supply the factors enumerated in Chart II.

This paper cannot cover all of the various diagnostic procedures and tests to help one determine these facts. You are, therefore, referred to the vast amount of literature on this subject, and should familiarize yourself with the pertinent facts to be obtained by physical examination, oscillometry, x-ray studies with and without contrast media in the arteries, temperature studies, ergometer studies and circulation time tests.

TREATMENT

Certain basic and almost self-evident features of treatment are applicable to all patients suffering from reduced arterial supply (Chart III).

Let me stress this first factor of rest. Since practically all patients in this group have varying degrees of spasm as a factor in reducing the blood flow, nervous tension must be eliminated as far as possible. It is not uncommon for me to have an intelligent business man come into my office complaining of intermittent claudication of a mild degree, but unduly alarmed by previous consultations as to the possibility of losing his leg. After a careful examination and reassurance he may report back a few days later for tests and, before treatment has been outlined, state

CHART III

PRINCIPLES OF TREATMENT

- 1. Rest
 - a. Mental
 - b. Physical
- 2. Optimum position of the extremity
- 3. Optimum environmental temperature
- 4. Elimination of factors reducing blood flow
- 5. Use of agents to increase blood flow
 - a. Reflex dilatation
 - b. Drugs
 - c. Hormones
 - d. Mechanical
 - e. Alterations in blood viscosity and volume
 - f. Foreign protein
- 6. Surgical procedures

that he can walk further and that his leg feels better. With reassurance his vasospasm associated with worry has become less.

Not only must we rest the mind, but we must not overtax the muscle or muscles with impaired nutrition. Where symptoms are early and reduction in blood flow is moderate, simple advice as to the amount of muscular activity is sufficient. Never let these patients force themselves against pain due to muscle ischemia.

In the more advanced cases where pain is present with rest or excessive emotion or cold, complete rest is just as important as it is in advanced pulmonary tuberculosis. The man with night pain or early gangrene needs weeks or months of complete freedom from use of the involved extremities and removal from the exciting causes of decreased blood flow when known. Any attempt to arbitrate this rule nearly always offsets the value of other treatment.

It is therefore apparent that it takes careful and intelligent handling of the individual to accomplish this rest without increasing the tension due to economic worries. Again, one of the problems of geriatrics rears its head unsolved.

Second: What is the optimum or ideal level at which to place the extremity with impaired arterial supply? Elevated, dependent or at heart level? There is no set rule. Here again a clear analysis of the problem is necessary. Let us take a theoretical case. Suppose we have a man with

obliterating arteriosclerosis and gangrene of the first toc. He has hypertension and his lesions are most marked peripherally. In his case the foot at heart level will probably receive the maximum supply of blood. If he has normal arterial pressure or hypotension, elevation of the head of the bed four to six inches will permit gravity to aid in supplying blood to the toes; but if he has large varicose veins, these will fill and prevent return of blood and stasis will result. This patient may be better off with a slight elevation of the foot of the bed.

Third: The proper environmental temperature for any given case is of utmost importance. It should be unnecessary for me to emphasize that extremities with impaired arterial supply are more easily frozen or burned than those with structurally and functionally normal arteries. All too frequently we see patients with burns of a serious degree following the unwise application of heat to the involved extremities. It is only natural when a patient has a cold extremity to warm it. However, if one applies heat by contact, radiation (infra-red) or by electrical energy (short wave or diathermy) serious results often follow. The leg with impaired blood supply is usually less sensitive to the recognition of excess heat. An infra-red lamp may blister or short wave may produce a deep burn before the patient is aware of it. Therefore, the only safe rule to follow is to avoid applying to the involved part direct heat greater than body heat. For most cases of arterial impairment, a cradle with a thermostatically controlled source of heat to maintain a temperature of 88° to 92° F. will produce the maximum circulation with the greatest degree of comfort.

Let us consider for a moment what happens when the temperature of an extremity is elevated by environmental heat. The metabolic rate of the tissues varies directly in proportion to the temperature. In other words, when the temperature is elevated metabolism increases and more blood is necessary. If the arterial supply is so damaged that the added demand cannot be met, pain increases and death of tissues may follow. Therefore, it follows that tissues supplied with badly damaged arteries should be kept at lower temperatures than those with better circulation.

Recently it has been found that if the air in the cradle surrounding a limb with an acute arterial shut-off, due to an embolism, is kept at low temperatures of 50° to 60° F, there will be less danger of gangrene and pain will be less marked. This can be accomplished by packing ice bags around the cradle and if necessary using a small fan to keep the cooled

CHART IV

FACTORS REDUCING BLOOD FLOW

- 1. Tight garters
- 2. Tight bandages
- 3. Tight shoes with rough interiors
- 4. Tight shirts and sweaters
- 5. Bad postures in occupations—leg over ladder rung—kneeling for long periods, etc.
- 6. Standing in one position for a long time
- 7. Repeated shocks or vibratory trauma
- 8. Tobacco and ergot

air moving over the leg. While this is being done vasodilatation can be accomplished by drugs and by reflex methods to be described later and the cardiac function improved. This type of therapy does not apply to thrombi lodging high in the thighs or in the iliac vessels where immediate embolectomy is indicated whenever possible. In summary, then, one might say that the more complete and sudden shut-offs need lower environmental temperatures than do the gradual incomplete closures.

Fourth: If in the management of peripheral arterial impairment problems it is our aim to increase blood supply, then one should carefully eliminate all factors which tend to diminish arterial supply. Some of these seem so self evident that I would hesitate to mention them except for the fact that I see referred patients frequently to whom such advice has been overlooked. It is not necessary more than to enumerate most of them (Chart IV).

Although ten years have passed since Maddock and Coller² demonstrated the vasospastic effect of smoking and although their work has been confirmed by numerous workers including members of our own clinic staff,³ many physicians are not being emphatic enough with their patients suffering from occlusive arterial diseases regarding the use of tobacco. I believe that all workers in this field are firmly convinced that tobacco is a powerful vasoconstrictor and that it must be eliminated completely from the habits of persons suffering from impaired blood supply due to arterial (and even venous) disease. Reduction in amount is not

adequate. The use of filters does not eliminate enough of the vasospastic factors and the so-called denicotinized cigarettes still produce a high degree of spasm. Cigar and pipe smoking is apparently as serious as cigarette smoking.

Although not directly associated with producing further impairment of circulation these individuals should be warned against trauma, cutting nails too close and the use of necrotizing salves and ointments containing salicylic acid, carbolic acid and iodine. Fungus infections should be treated by soaks of non-irritating substances like potassium permanganate 1:4000 or 1:8000 at body temperature.

Again, let us look at the patient as a whole especially as to the cardiovascular system. If there is heart involvement, if the patient is overweight, if he has other debilitating disease, treat these problems along with those in the extremities.

Fifth: I have left the most dramatic angle of therapy and the one we usually think of first as the final problem of discussion under the management of reduced arterial supply. What means have we available to increase blood flow where the damage is for the most part localized to an extremity? Methods effectual in overcoming spasm are of little value in obtaining more blood through vessels with narrowed lumens due to disease of their walls. So again let me emphasize the importance of evaluating the process. Where spasm predominates, vasodilating mechanisms are indicated. Reflex methods of vasodilatation are of great help. By heating the upper extremities in hot baths or by applying electric pads to the back and abdomen, or by using diathermy or short wave to the trunk to increase body temperature, peripheral vessels in spasm in the involved lower extremity are reflexly opened and the blood supply increased.

Drugs (Chart V) have relatively little value in producing vasodilatation of the blood vessels in an extremity. The nitrites and the purine derivatives either have no demonstrable effect or their systemic effect is so marked that a drop in blood pressure offsets any beneficial effect. Recently papavarine in large doses of 1 and 1½ grs. has been reported by Elek and Katz⁴ as effectual in producing vasodilatation in peripheral vascular disease. In a personal communication from Dr. Mulinos⁵ of the College of Physicians and Surgeons of Columbia University I have been informed that the spasm of Raynaud's syndrome could be overcome with this drug.

CHART V

DRUGS USED IN THE TREATMENT OF ARTERIAL DISEASES

| | Action | | |
|------------------------|--------------------------------------|--|--|
| Iodides | On cholesterol metabolism? | | |
| Arsenic Bismuth | On syphilis | | |
| Sulfonamides | On infections | | |
| KMnO, | Fungicide | | |
| Opiates | To relieve pain and spasm (reflexly) | | |
| Salicylates | To relieve pain and spasm | | |
| Xanthanes | To relieve spasm | | |
| Nitrites | To relieve spasm | | |
| Alcohol | To relieve spasm | | |
| Histamine Cholines | To relieve spasm | | |
| Adrenalin Ephedrine | To increase tone | | |
| Phenylhydrazine | To reduce the red blood count | | |

Drugs which relieve pain of peripheral arterial insufficiency may be of value in increasing circulation by eliminating reflex spasm. Pantopan and the salicylates are useful in this sense. Combinations of vasodilating drugs and sedatives have even greater effect than either alone.

Whiskey in small amounts often causes a slight dulling of pain and probably some slight vasodilatation. However, in sufficient quantities to produce signs of intoxication, a reduction in blood flow to an extremity has been demonstrated by Veal.⁶

Hormones have been tested for several years to determine their status in producing vasodilatation.

Thyroid extract increases blood flow but also increases body metabolism and its use is of questionable value.

' Very little work has been done on pituitary extracts and none are known to be of value.

The androgens and estrogens* have been reported by various workers to increase coronary and possibly peripheral blood flow. Whether

Supplied to us by Ciba & Company for experimental work (Diovycylin and Perandron).

this effect is a result of a direct action on the peripheral vessels or an indirect one by overcoming tenseness in the nervous system is still undecided.

Certain tissue extracts promise even more efficient hormonal activity. Although pancreatic extracts have been available for nearly ten years there is still much disagreement as to their value and what is more as to their mode of action. We have had considerable experience in the Vascular Clinic of the New York Post-Graduate Hospital with several of these preparations. There is one significant observation borne out by clinical tests. Intermittent claudication associated with occlusive arterial disease is definitely benefited by their use. Walking distance is increased in some instances by considerable amounts. Recent articles by Fatherree and Hurst, Klein, Saland and Zurrow substantiate this observation. However, there is so far little evidence to support their value in the relief of rest-pain or in the healing of gangrenous lesions.

In animal work a direct effect on blood pressure can be demonstrated suggesting vasodilatation. One product* is standardized by noting its effect on the blood pressure of the dog. One unit of this material will depress the systolic blood pressure to the same degree that I mgm. of adrenalin will elevate it in the same animal. Unfortunately, all of these substances have to be administered hypodermically. The usual dose is 3 cc. intramuscularly three times a week. The patient can be taught to give the injections as easily as one would give insulin. We have seen many patients, in whom intermittent claudication is the predominant symptom, able to do much more work while using this form of therapy.

Cholines may be considered as hormones and again we have had extensive experience with their use. There are many forms available for therapy. Acetyl choline is mild in its action while Acetyl B methyl choline hydrochloride** is about 100 times more potent. They are of little value when taken orally and when given hypodermically produce such marked vasodilatation that vasomotor collapse may result. Some years ago we therefore developed a method of applying them locally by galvanic current (iontophoresis) in the treatment of vasospastic diseases affecting especially the skin. They are of real value in healing superficial ulcers due to impaired arterial supply and associated arteriolar spasm.

^{*} Depropanex supplied to us for experimental purposes by Sharpe & Dohme.

** Supplied to us by Merck & Company since 1935 for experimental purposes

Examples of such pathology are ulcers associated with varicose veins and in some cases ulcers associated with arteriosclerosis. Recently we have treated a few patients by simply spraying a 1/5 per cent solution onto the ulcer with satisfactory results until the ulcer is about healed. It would appear that the galvanic current is necessary to cause absorption of the drug through the unbroken skin. For the technique of iontophoresis I would refer you to a paper by Kovacs.⁹

Mechanical methods of increasing blood flow have flooded the medical apparatus market. Since Buerger¹⁰ described his method of postural exercises, various means have been devised to apply this principle. Most of these are accomplished by active effort on the part of the patient and when the blood supply is not too impaired such an application of the method is wise. However, where the exertion necessary to carry out the exercises increases the pain a passive method is indicated. Several types of apparatus have been developed to accomplish this but the most satisfactory one from our experience is the oscillating bed of Sanders. This permits drainage and filling of peripheral leg vessels by gravity without effort on the part of the patient and over long periods of time even to twenty-four hours a day. Through adjustments the rate of the cycle and the degree of dependency and elevation of the foot can be altered. Such adjustment to meet each patient's needs is extremely important. The foot should be in the elevated position long enough and high enough to produce slight pallor only and in the dependent position to produce slight rubor. A faulty adjustment which tends to decrease the amount of blood supply by keeping the leg elevated for too long a period may actually cause more pain and a progression of a vascular lesion.

Since such a therapeutic method has little effect on spasm, it should be used together with a heat cradle set for an optimum temperature, reflex vasodilating methods and drugs in order to obtain maximum blood flow.

Intermittent venous occlusion, as described by Collens and Wilensky¹¹ and by Linton,¹² is based on the principle that there is a reflex dilatation and increased blood flow in the arterial system as a result of this intermittent interference with the venous return. This method would therefore be of value only where vasospasm is a major factor and would be of little help where organic changes predominate. There is still considerable controversy as to its value as a mechanical form of therapy.

The same may be said for the "boot" in which an involved extremity is placed and the pressures in the boot are alternately increased and decreased above and below atmospheric level. Here again such pressure changes should be just sufficient to produce pallor and rubor and the period of pallor should not be too long. The cuff which maintains the pressure and which fits around the thigh or arm must be tight enough to avoid the leakage of air but not so tight as to obstruct venous return. Moreover, in many instances collateral blood flow is located near the surface of the extremity and a poorly applied cuff may interfere with this supply.

Recently we have been experimenting with a vibrating table in which there are alternate long and short vibrations with the extremity so placed that the dynamic effect would force blood peripherally. The method is simple and is easily applied but it is still too new to report on its effect. In persons with a sensitive sympathetic nervous system a reflex spasm from the vibrating factor may offset its value.

Before leaving the discussion of mechanical aids I would like to stress the point that most patients suffering from arterial disease can be successfully treated without the use of such methods. Moreover, when they are used they must be thoroughly understood and each patient must be studied while receiving such treatment to be sure that the therapy is of value and, what is more important, that the apparatus is properly applied and adjusted.

Various investigators have attempted to treat occlusive and vaso-spastic arterial problems by attempting to alter the blood volume or viscosity. One of the earliest forms of such therapy was the instillation of large amounts of Ringer's solution by duodenal tube. This method naturally had many undesirable side-effects. Later Bernheim¹³ suggested the use of 250 cc. of 2 per cent sodium citrate solution in an attempt to reduce blood viscosity and, more recently, Theis and Freeland¹⁴ have been using sodium tetrathionate. All such methods are helpful but for the most part necessitate intravenous therapy which is expensive and time-consuming and which may be complicated by reactions if one is not careful in administering these infusions.

The same objection may be brought forward regarding the use of hypertonic saline solution of 3 per cent or 5 per cent and of 300 to 500 cc. volume. Although such intravenous therapy has been shown to increase blood flow into an extremity and lead to healing, especially in

thromboangiitis obliterans, I feel that simpler methods can accomplish the same result.

An example of a simpler method for producing vasodilatation is demonstrated by foreign protein reaction. Intravenous injections of carefully measured doses of plain typhoid vaccine, starting with 3 to 5 million organisms will produce vasodilatation lasting 12 to 36 or even 48 hours. Sulphur in oil or milk given intramuscularly will produce the same result but the dose is hard to regulate and the pain produced makes the use of these reagents unsatisfactory. When intravenous typhoid vaccine is used the dose can be repeated every 72 to 96 hours increasing it gradually to give a slight temperature reaction but without chill.

Sixth: I shall not attempt to deal at length with the surgical procedures of value in the management of arterial diseases. Pratt¹⁵ recently read a paper on this subject before this group.

Amputation will usually be avoided by the careful management of a patient as above outlined. However, when it becomes apparent that it is necessary, do not delay. Choose your site so that secondary amputation will not be needed and prepare your patient to avoid shock and thereby perhaps precipitate a sudden closure and gangrene in another extremity.

Interference with the sympathetic supply by novocaine or procain injections of the nerve roots supplying the affected extremity will often give maximum vasodilatation for a period long enough to turn the tide from a progressing lesion to an arrested one. Furthermore, severance of peripheral sensory nerves will relieve pain and its reflex vasospasm and cutting of the sympathetics will give permanent vasodilatation and is the surgical procedure of choice where a chronic vasospastic major factor is the problem to be overcome and where other forms of less radical therapy have failed. A typical example of such a problem is a severe Raynaud's syndrome.

In a discussion on the management of peripheral vascular diseases one cannot conclude his remarks without spending a few minutes on the anticoagulants. Since Murray and Best¹⁶ described heparin and Link and his co-workers¹⁷ dicoumarin, a great deal of work has been done with these substances. Previous to these discoveries leeches and extract from leeches had shown some value as anticoagulants.

In arterial disease the problem confronts us as to when to turn to these potent agents. Since heparin exerts its effect rapidly and dicoumarin, which is usually given orally, takes 24 to 48 hours to produce a

delay in coagulation, one can be guided in his selection of reagents by these facts. Therefore, in embolic problems with the danger of superimposed ascending thrombosis and in arterial surgery heparin must be used, since in 48 hours fatal thrombosis may have occurred. However, in chronic diseases such as thromboangiitis obliterans with a thrombotic problem, dicoumarin is preferable. As we understand the action of these substances we may find that a combination of the two may be most satisfactory, starting with heparin to get its immediate effect and following it with dicoumarin to conclude the course of anticoagulant therapy. Heparin is expensive at present, has to be given by continuous infusion, which is annoying to the patient, and its effect must be watched by frequent coagulation time tests. Dicoumarin on the other hand is cheap, can be given by mouth and the alterations in the prothrombin and coagulation times are less rapid and therefore tests for these functions on the blood do not have to be carried out as frequently. However, when heparin is discontinued its effect is over in a few hours while dicoumarin maintains an increase in the coagulation time for days. Transfusions of whole blood will however stop the anticoagulant effect of dicoumarin if the coagulation or prothrombin times become too prolonged. Banked blood loses its thrombokinase and is therefore of no value in stopping the action of dicoumarin.

Until such time that these substances are better known, especially dicoumarin, I believe the average physician, inexperienced with their use, should have guidance in treating a patient with them. Excessive bleeding, especially renal in origin, may occur if too great a dosage is used.

In addition to the problems mentioned, the anticoagulants may prove of real value in preventing mural thrombosis in coronary disease, in limiting thrombotic lesions in vegetative endocarditis and thereby reducing the possibility of pulmonary or peripheral embolism. Wright and Prandoni¹⁸ have demonstrated the value of dicoumarin in the treatment of thrombophlebitis.

Management of Venous Problems

Venous pathology of the extremities is chiefly on an organic basis. Although the veins have the power to dilate and contract, this function is perhaps less important than it is in the arterial side of the circulation. The main problems confronting us are shown in Chart VI.

CHART VI DISEASES OF THE VENOUS SYSTEM

- Varicose veins

 Congenital
 - b. Acquired
- Distended—pulsating veins

 Due to arterio-venous anastomosis
 - b. Due to tricuspid insufficiency
- III. Phlebitis
 - a. Acute
 - b. Chronic
 - c. Migratory
- IV. Thrombosis
 - a. Primary
 - h. Secondary

Varicose veins when definitely developed are a problem for surgical procedures. Only minor vessels can be successfully eradicated by local injection therapy. Unfortunately, many patients have received repeated injections of various sclerosing solutions into large vessels with little or temporary relief. It has been demonstrated that many of the thrombotic lesions produced by local injections are absorbed within a few months and the veins are as varicose as previous to therapy; sometimes, even more so.

It is therefore evident that in all cases of varicosities of even moderate degree, and especially in those in which the saphenous vein is distended by back flow from the femoral vein, surgical ligation with resection and retrograde injection is the procedure of choice. In addition to the above procedures, all incompetent communicating vessels from the groin to the lower leg must likewise be ligated to prevent the future development of local venous distention and varicosities at such sites. Again I leave the description of the technique to the surgeon.

The general practitioner and the internist must, however, be able to select those patients whose therapy is surgical. He must be familiar with the tests to demonstrate back flow through superficial veins such as the Trendelenberg test and its modifications. It is of the utmost importance that he test his patient for competent deep vein function. The Perthes test is easily and simply performed and in 15 to 20 minutes one can determine the patency of the deep veins. The leg is bandaged from the ankle to the groin with an elastic type of bandage applied tight enough

to obliterate superficial veins and still permit arterial pulsations to be obtained at the foot. The patient should be able to walk for 15 minutes without cyanosis of the foot or pain anywhere in the leg. Either of these signs or symptoms is a contraindication to obliteration of the saphenous system.

One is likewise frequently confronted by the problem of complicating arteriosclerosis. It has been our experience that in ambulatory patients the obliteration of the veins is beneficial. However, in patients with arterial lesions so advanced that gangrene is present or imminent, venous back-pressure is usually not a factor as, with bed rest, drainage is usually adequate. However, if these patients develop collateral arterial circulation and become ambulatory, then removal of the venous pools becomes necessary.

All patients with varicose vein problems must be studied carefully to rule out diabetes and, if present, it must be controlled before surgery is undertaken. The same holds true for syphilis.

The question also arises as to the wisdom of operating on varicose veins complicated by phlebitis. Certainly the best rule to follow is to avoid surgery until evidence is obtained that any such process has subsided. The erythrocytic sedimentation test is a helpful guide in determining activity of phlebitis.

There has been a tendency in recent years to ligate the femoral vein in certain cases of deep phlebitis. In reviewing a series of cases in which this was done and comparing the results with less radical therapy, I could find no decrease in the incidence of pulmonary emboli or quicker recovery from the phlebitis. Moreover, there is the definite possibility of some permanent edema because of this procedure.

A few words must be directed at an unusual but interesting phenomenon, that is, pulsating veins. In any patient with distended veins, always watch for pulsations. In making this observation elevate the extremity above heart level. In so doing varicose veins should collapse, while vessels filled with arterial blood remain distended. The sterhoscope frequently will locate the anastomosis between the artery and vein with the revealing of a bruit. In rare instances the veins of one or both lower extremities will pulsate with back flow from a tricuspid insufficiency.

Phlebitis is one of the problems of peripheral vascular disease which is usually easily diagnosed but is frequently exceedingly resistant to therapy.

It may be unnecessary repetition but the prophylaxis of phlebitis is really of greater importance than its treatment. In every surgical procedure every possible means should be used to maintain rapid and full blood flow through the extremities, especially the lower ones. We have only time to enumerate such means. The patient should be made to breathe deeply on return from the operating table, either by the use of CO₂ inhalation or by injections of coramine. Tight constricting bandages must be avoided and the extremities must be kept warm. If there is question of shock, elevation of the foot of the bed is imperative and the replacement of blood volume with plasma or blood is urgent. In healthy individuals presurgical thyroid medication will speed up blood flow and in patients with cardiac disease adequate therapy directed at poor cardiac output must be given. Anticoagulant therapy in individuals with a history of previous embolic accidents or phlebitis may in the future be a routine postoperative procedure.

When we are faced with the treatment of phlebitis itself, certain principles of therapy must be carried out. Again, we do not have time to discuss in detail each principle. However, this paper would not be complete without some time on this important problem.

Many of the principles of prophylaxis may be applied to the treatment of the active process. Since the etiology of phlebitis is still confused and the processes not clearly understod, many of our present forms of therapy may be discarded in the future. However, at present the following procedures seem to promote the most rapid healing.

- 1. Use all means to promote rapid blood flow through the involved extremity, such as hot packs for 18 to 24 hours a day, vasodilating procedures, especially paravertebral nerve-block, elevation of the extremity and the use of thyroid by mouth. Although I personally am not in favor of tight bandaging and active exercise, such as walking, some workers advocate this.
 - 2. Removal of foci of infection, especially fungus infections.
- 3. The treatment of the infection itself by chemotherapeutic drugs such as the sulfonamides and arsenicals and bismuth.
- 4. The use of anticoagulants such as heparin and dicoumarin. This form of therapy is certainly indicated in those patients prone to throw off emboli or in those in whom the thrombotic lesions predominate. Again, I suggest you turn to the paper of Wright and Prandoni published in the Academy Bulletin last year for the details of such therapy.

Before leaving the problem of phlebitis let me discuss briefly the annoying symptom of neuritis that frequently accompanies this process. Since we know that the pathological process frequently involves the perivascular tissues, it is evident that in healing, the sensory nerves accompanying the vessels may become irritated and pain may result. Many patients still have considerable pain along the course of the veins long after the acute process has subsided. When one is convinced that activity of the process no longer exists, then massage, baths and active exercises are indicated. Extra vitamin "B" in the entire complex may be of real value during the active and arrested stages of the disease.

Finally, a word or two about non-inflammatory venous thrombosis. This is usually secondary to some chronic pressure or perhaps to an invading new growth, although one occasionally sees a patient with thrombi developing in various parts of the venous system without evident cause. The treatment of such problems is naturally first to remove the cause, if known, and secondly to increase blood flow by the means used in the treatment of phlebitis.

DISEASES OF THE LYMPHATICS

Of the three vascular systems in the extremities we probably know less about the lymphatics than we do of the arterial and venous channels. There is a superficial and a deep system of lymphatic vessels in the legs but unlike the veins they do not communicate except through the popliteal and inguinal areas. All of the lymphatic drainage from the leg, superficial and deep, joins below Poupart's ligament and runs closely to the veins, even being enclosed in a tough fibrous sheath beside the vessels.

In the upper extremity, the lymph drainage system is more complicated, but all vessels drain through the axillary lymph nodes. As in the venous system, obstruction to a large vessel is followed by drainage through collateral vessels. If the cut ends of a severed vessel are approximated, regeneration takes place and the vessel resumes function. The regeneration of the vessels is rapid. An incision is bridged in four days and by the eighth day regeneration is adequate to carry lymph.

The flow of lymph through these channels is controlled principally by muscle contraction. Valves in the system keep the flow moving proximally. Flow is fairly rapid under normal circumstances and probably takes only a minute or so to pass from the foot to the larger vessels in the abdominal cavity. Lymph clots more slowly than blood (normally in 10-20 minutes) due to a deficiency in thromboplastic substances.

The diseases affecting these channels may be divided into two main groups; first, inflammatory and second, obstructive. This second group may be the result of congenital defects, pressure on, or destruction of the lymphatics, or due to chronic infection.

Acute lymphangitis usually subsides with little residual edema but if diffuse, chronic or recurrent, permanent damage may result with lymphedema as the end result. The management of lymphatic problems is therefore largely one of prophylaxis. An acute infection or injury to an extremity may be the beginning of permanent lymphatic damage. Let me cite a recent instance. A worker received a crushing injury to his right fourth finger with a secondary infection at the base of the digit. This responded to surgical drainage but not before the hand and forearm had become red and swollen. The complicating lymphangitis became chronic and after four years this man has destruction of many of the lymph channels draining his right hand with permanent disabling edema.

Allen and Ghormley¹⁹ have stressed this important fact of prophylaxis so let me spend some time pointing out the important procedures indicated in any patient liable to develop a lymphedema.

Elevation should be immediately ordered and the involved extremity kept in such a position until all signs of infection have cleared or the injury healed. No matter what produces the edema the mechanism leading to a permanent swelling is always about the same. Pressure in the lymph spaces increases with a resulting dilatation of the vessels, destruction or incompetency of the valves. This in turn produces further stasis. In this static lymph fibroblasts proliferate and this in turn further slows the flow and secondary inflammation may occur with further fibrosis and scar formation. By elevation we permit rapid drainage from the extremity, keep the valves competent, prevent fibrosis and thereby prevent permanent damage.

Eradication of infection is clearly as important a step as elevation because the patient is potentially a bed case until this is done. With the discovery of the sulfonamides we have valuable chemotherapeutic agents to help eliminate the usual invader, the streptococcus. However, many workers now feel that fungus infections, epidermophytoses, may be invading agents or at least open the portal of entry for bacterial in-

vaders. Therefore, their elimination is important and their prophylaxis even more so.

Venous stasis due to varicose veins is often a cause of chronic edema through such a mechanism as I recently described. Therefore, every patient with varicose veins is a potential sufferer from lymphedema and such veins should be eradicated. The danger of this complication is even more marked if a complicating phlebitis occurs. Phlebitis without varicosities may likewise have an associated lymphangitis and a secondary lymphedema.

Filiariasis, although rare in this part of the world, is a well-known cause of elephantiasis and must not be overlooked in patients who have lived or travelled in parts of the world where this parasite is found.

Systemic disease may produce temporary edema which, if the disease is not treated, may become chronic lymphedema. Heart and renal insufficiency are the usual causes of swelling but hypoproteinemia must not be overlooked.

One must not forget that carcinoma, surgical removal of lymph glands, x-ray therapy and chronic pressure or long dependency of extremities are other causes to be eliminated wherever possible.

However, there is one group of patients with lymphatic obstruction on the basis of what appears to be a congenital defect in the lymphatic system for which there is little to be done from the prophylactic angle. Such cases have been called primary lymphedema, precox and congenital (Milroy's disease when occurring in families). Many of these do not appear until about the age of puberty.

In all cases of edema, regardless of the cause, when the patient becomes ambulatory, support of the tissues in the involved extremity must be carried out, often for a long time, until it is evident that the edema will not recur when such support is removed. Bandages, rubber, woven elastic, adhesive and non-adhesive or stockings may be used but the support must be adequate to control the swelling without blocking the arterial supply.

I have been able to demonstrate in several early cases of the congenital type of lymphedema, that after dehydration and elevation of the extremity to reduce the edema, adequate support over several years will help the growth of collateral vessels sufficiently to prevent edema.

When frank lymphedema of marked degree has developed, medical treatment can be of little avail. Removal of the fibrotic edematous lym-

phatic tissue by some form of a Kondoleon operation is the only surgical method giving results that are satisfactory. The actual technique I shall leave to the surgeon. However, medically these patients should be prepared by elevation of the involved part and dehydration to remove as much of the fluid as possible. Sulfonamides should be given for 3 to 4 days to sterilize the tissues, which often contain streptococci, and immediately postoperatively blood or plasma must be given to prevent shock.

In one hour's time I have been barely able to touch upon the principles behind the management of the diseases affecting the peripheral circulation. I hope I have stimulated your interest in this field.

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DIETARY TREATMENT OF LAENNEC'S CIRRHOSIS WITH SPECIAL REFERENCE TO EARLY STAGES OF THE DISEASE*

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cirrhosis resides in our ignorance of the nature of the disease. In searching for factors that predispose to cirrhosis and which thus may bear upon its etiology one fact remains glaringly prominent, namely, that alcoholism is the most common antecedent factor in this disease in the Western hemisphere. I shall not cite the evidence for this observation, which is common knowledge. And yet, in about 30 per cent of cases seen at postmortem examination there has been no story of alcoholism. Or, if one examines data on chronic alcoholism, one finds that only a small per cent, variously estimated at from 1 to 25 per cent, develop Laennec's cirrhosis. It seems very probable that the association is intimate, but not direct; that alcoholism per se does not cause cirrhosis of the liver.

Since alcoholic beri-beri^{1,2} and pellagra³ have been shown to be similar to the endemic forms of these diseases, it seemed possible that the correlation between alcoholism and Laennec's cirrhosis also might be due to co-existing nutritional deficiency. This hypothesis seemed attractive, particularly since a high incidence of vitamin B complex deficiency was noted in our patients with this disease, and also has been reported by others. ^{4,5,6} With this in mind we started treating patients with Laennec's cirrhosis by means of a highly nutritious diet supplemented with vitamin B concentrates, and reported favorable results in a series of thirteen patients. ⁷ However, since the patients were observed for only one year, it seemed advisable to extend the program over a longer period of time in a larger number of patients. This we have done during the past five years.

Meanwhile, from different laboratories, experimental evidence has

^{*} Read December 15, 1942 before the Section of Medicine of The New York Academy of Medicine.

TABLE I
CLINICAL DATA ON PATIENTS WITH LAENNEC'S CIRRHOSIS*

| | Treated S | Series (54) | Control Series (386) | | |
|---------------------|-----------|-------------|----------------------|----------|--|
| | number | per cent | number | per cent | |
| Symptoms | | | | : | |
| Weight loss | 42 | 78 | 206 | 53 | |
| Abdominal Swelling | 48 | 89 | 301 | 80 | |
| Peripheral Edema | 46 | 85 | 236 | 61 | |
| Nausea and Vomiting | 29 | 54 | 129 | 33 | |
| Hematemesis | 13 | 24 | 106 | 27 | |
| Abdominal Pain | 22 | 40 | 121 | 31 | |
| Signs | | | | | |
| Ascites | 48 | 89 | 301 | 80 | |
| Palpable Liver | 44 | 81 | 291 | 7.5 | |
| Palpable Spleen | 38 | 70 | 170 | 4-1 | |
| Jaundice | 31 | 63 | 252 | 65 | |
| Edema | 46 | 85 | 236 | 61 | |
| Hemorrhoids | 30 | 56 | 105 | 27 | |
| Collateral Veins | 41 | 76 | 91 | 23 | |
| Vascular Spiders | 37 | 68 | 58 | 15 | |

accumulated which supports the hypothesis of a nutritional component in the pathogenesis of cirrhosis. Recent studies indicate that the feeding of yeast, s, of protein, lo, 11, 12 and of choline may afford a degree of protection against known liver poisons. Other studies suggest that the lack of certain factors contained in yeast or casein brings about fibrotic changes in the livers of rats 14, 15, 16, 17 and rabbits. The feeding of excess fat 19, 20 and of excess cystine also is said to produce liver cirrhosis in experimental animals. Although all these observations do not fit neatly into a single concept of the disease process, it is possible that the differences can be reconciled. The significance of these studies in relation to human Laennec's cirrhosis awaits further clarification.

So much for the evidence of a nutritional factor in the etiology.

^{*} Condensed from previous publications (references 22, 23).

I wish now to describe some of our clinical findings; first in the treatment of patients with frank liver failure or decompensation, and second, with a group of patients who were considered to show signs of early liver damage. This work has been carried out in conjunction with Doctors Joseph Post²² and Oscar D. Ratnoff.²³

The first group comprises a series of fifty-four patients with decompensated Laennec's cirrhosis. By decompensated I mean that there were signs of frank liver failure, which required hospitalization. In order to establish a norm for comparison with this treated group, a series of 386 cases of cirrhosis was analyzed from the records of five New York hospitals. These will be referred to as a control group. Clinical data obtained from these two groups are recorded in Table I. Several of these symptoms and signs showed a higher incidence in the treated series than in the control series, due presumably to the fact that our patients were under close scrutiny for longer periods of time. However, it seems fair to conclude that the symptoms and signs were comparable in the two groups, and that the severity of the underlying disease process also was comparable.

In contrast to the usual American diet prescribed for liver disease, which is high in carbohydrate but low in protein and fat, the present diet is rich in protein and ample in carbohydrate and fat. It contains 3,591 calories and it has the following proportions: Protein 139*, Fat 175, Carbohydrate 365. The diet consists chiefly of meat, milk, eggs, fruit, and green vegetables. Meat is served twice daily; milk five times daily-three times with meals and two times with 25 grams of powdered brewer's yeast. It is advisable to feed the yeast in graded, increasing doses up to the final amount. Occasionally patients cannot tolerate brewer's yeast. For these, oral vitamin B complex has been substituted in the form of liquid yeast concentrates. In addition, thiamin chloride (5 mgm.) is injected i.m. daily and liver extract (5 cc.), twice weekly. The art of nursing is put to the test, for it involves feeding a patient to whom food often is loathsome. Regard for his likes and dislikes, encouragement, and infinite patience are needed. The nursing and dietetic care, particularly during the critical period of decompensation, should be as meticulous and vigilant as that given the patient with typhoid fever. The intake of each meal should be charted in order to keep ac-

^{*} Includes protein in brewer's yeast.

count of the actual consumption. It is the amount consumed rather than the amount served that counts.

In patients with ascites the salt intake is restricted only by the exclusion of a salt shaker from the tray, and fluids are allowed up to 2000 cc. daily. Too rigid restriction of salt and water is harmful to these patients, and has been observed to precipitate symptoms of hypochloremia. It should be realized that with each abdominal tap considerable salt is removed. Nonetheless, it is desirable to tap abdominal fluid before the patient is distended too much, for this interferes seriously with the appetite. Mercurial diuretics may be injected once or twice weekly together with ammonium chloride by mouth, in order to space out the intervals between paracenteses.

For the sake of simplicity in discussing results of this treatment, the patients were placed in three groups according to their clinical course:

Group A: Those patients who showed signs of progressive failure. There were twenty-two in this group. Of these eleven died within one month, and only four survived more than 5 months after entry to the hospital. It is evident from this short period of survival that they were severely ill at the time of admission.

Group B. Those patients who made partial improvement. There were twelve in this group. Five showed satisfactory improvement, as gauged by the loss of ascites and by changes in their laboratory tests, but they were classified in this group because of a limited follow-up after discharge from the hospital. Three others have remained free of ascites, after having required abdominal taps in the past, but they are not in robust health. Four others made similar improvement, but they subsequently died, after being ascites-free for over 2 years in each instance.

Group C. Those patients who showed signs of "clinical recovery." Their improvement fulfilled three criteria: (1) Gain in weight and strength permitting the patient to resume his previous activity; (2) loss of ascites, edema, and jaundice without recurrence; (3) changes of serum proteins, Takata-Ara, and bromsulfalein dye tests towards normal values.

By this I do not wish to imply that the laboratory tests of this latter group were completely normal, nor that the histological changes were reversed. However, it was clear that the process had been arrested, or reversed to a degree that allowed the patient to live a normal life for several years. There is no doubt that there will be relapses, and that as a group their life span may be shorter than that of persons who have not had the disease.

In order to determine whether treatment altered the course of the disease significantly, comparison was made with the control series of 386 patients previously mentioned. It was shown that approximately 7 per cent of the control series, in contrast to 60 per cent of the treated series, experienced the spontaneous disappearance of ascites. The period of survival of patients after the onset of ascites showed the following differences: At six months 57 per cent of the controls were alive in contrast to 72 per cent of the treated series; at one year there were 37 per cent of the controls and 57 per cent of the treated series; at two years there were 22 per cent of the controls and 45 per cent of the treated series.

The data on these fifty-four patients were obtained from 1936 to 1941, and they are reported in detail in a previous publication. Although the series has been increased by many patients in the past two years, our subsequent experience has been much the same. From the Mayo Clinic, Fleming and Snell²⁴ recently reported encouraging results in fifty cases of decompensated Laennec's cirrhosis, treated with a high protein diet together with vitamin concentrates. Twenty patients (44 per cent) showed significant clinical improvement. Of this group, ascites had disappeared in eleven, and had diminished in five. Keefer and Fries²⁵ recently described seventy cases of "fatty liver." Of these, nineteen were latent cases, whereas fifty-one showed signs of hepatic insufficiency, such as jaundice and ascites. The authors believe that a high carbohydrate, low fat, medium protein diet together with vitamin concentrates is of therapeutic value.

Since our series of fifty-four patients had arrived when liver damage was extreme, there was little hope of obtaining a high per cent of clinical recoveries. However specific this or any other treatment may be, the success will be limited until the disease is diagnosed earlier. Therefore, we have tried to recognize earlier stages of the disease, even though the means of diagnosis are still inadequate.

The high incidence of nutritional deficiency, especially of the vitamin B complex, in Laennec's cirrhosis suggested that a nutritional factor might play a role, and treatment was based upon this hypothesis. It therefore seemed possible that patients who entered the hospital be-

TABLE II

SIGNS OF MALNUTRITION IN 88 PATIENTS WITH VITAMIN DEFICIENCY
DISEASES AND IN 54 PATIENTS WITH LAENNEC'S CIRRHOSIS

| | Vitamin De | ficiencies (33) | Laennec's Cirrhosis (54) | | |
|----------------|------------|-----------------|--------------------------|----------|--|
| | number | per cent | number | per cent | |
| Weight Loss | 21 | 61 | 42 | 78 | |
| G. I. Distress | 18 | 55 | 29 | 54 | |
| Polyneuritis | 26 | 79 | 21 | 40 | |
| Smooth Tongue | 23 | 70 | 32 | 60 | |
| Dry Skin | 19 | 60 | 31 | 63 | |
| Macrocytosis | 12 | 36 | 21 | 40 | |

cause of malnutrition alone would show signs of occult liver damage. We selected those who entered because of polyneuritis, sprue, pellagra or scurvy, but without overt signs of liver damage such as jaundice, ascites, or edema. However, since these patients were sent to us from clinics that knew of our interest in liver disease, the selection of these patients undoubtedly was biased. It is also unfortunate that the majority were alcoholics, but in this climate it is difficult to divorce nutritional deficiency from alcoholism. Despite these objections the data are of interest.

In Table II the incidence of signs of malnutrition in thirty-three patients with vitamin deficiency diseases is compared to that of fifty-four patients with Laennec's cirrhosis. There is a close similarity between the two groups.

In Table III are listed the signs of liver damage in the same groups of patients. There is similarity here as well, but also several distinct differences. Splenomegaly and vascular "spiders" were seen commonly only in the mature form of Laennec's cirrhosis. Hypoalbuminemia occurred in 33 per cent of the group with vitamin deficiencies in contrast to 96 per cent of those with cirrhosis. However, elevated serum globulin, increased bromsulfalein dye retention and positive Hanger flocculation reactions appeared commonly in both groups of patients. Hence, the latter three tests may be considered to be sensitive indices of liver damage.

TABLE III

SIGNS OF LIVER DAMAGE IN 33 PATIENTS WITH VITAMIN DEFICIENCY
DISEASES AND IN 54 PATIENTS WITH LAENNEC'S CIRRHOSIS

| • | Vitamin Def | iciencies (33) | Laennec's Cirrhosis (54) | | |
|--------------------------|-------------|----------------|--------------------------|----------|--|
| | number | per cent | number | per cent | |
| Palpable Liver | 16 | 48 | 44 | 81 | |
| Palpable Spleen | 2 | 6 | 38 | 70 | |
| Epistaxis | 7 | 21 | 25 | 46 | |
| Vascular "Spiders" | 3 | 9 | 37 | 68 | |
| S. Albumin < 4 gms. % | 11 | 33 | 52 | 96 | |
| S. Globulin>3 gms. % | 21 | 64 | 45 | 83 | |
| *Bromsulfalein>10% | 28 | 85 | 59 | 96 | |
| Positive Floce. Reaction | 14 | 64 | 4.9 | 91** | |
| No signs | 4 | 12 | | | |

^{*} Retention of bromsulfalein eye at 1/2 hr. Method employs 5 mgm/kilo.

TABLE IV

DATA ON PATIENT D.T. INDICATING TRANSITION FROM EARLY TO DECOMPENSATED STAGE OF LAENNEC'S CIRRIOSIS

| Adm. Disch. O.P.D. Adm. 6/40 9/40 5/41 9/42 11/42 1/43° Palpable Liver ++ + + ++++ ++ | · · · · · · · · · · · · · · · · · · · | 1st I | 1st Entry | | 2nd Entry | | | |
|---|---|---------------------------------------|-------------------|--|--|---------------------------------------|---------------------------------|--|
| Palpable Liver Palpable Spleen Vascular "Spider" Jaundice Ascites S. Albumin gms. % S. globulin gms. % Bromsulfalein % | | Adm. | Disch. | O.P.D. | Adm. | | | |
| | Palpable Spleen Vascular "Spider" Jaundice Ascites S. Albumin gms. % S. globulin gms. % | ++ 0 ++ 0 0 4.4 2.9 | + 0 + 0 0 4.3 2.6 | + 0 + + 0 0 0 4.1 4.0 64 | +++ + + + + +++ 2.9 2.8 70 | ++ + 0 0 3.7 3.3 60 | ++ + 0 0 4.1 2.9 | |

^{*} Data obtained since presentation on 12/15/42.

^{**} Takata-Ara reaction.

The question may be raised as to whether such cases actually represent an early stage of Laennec's cirrhosis. I believe that they do. As an example, I wish to describe the findings in a patient who was observed for 2½ years and whose course showed a transition from the early "subclinical" to the decompensated stage of Laennec's cirrhosis (cf Table IV).

Case History: A 43 year old entertainer gave a story of alcoholism and a meagre diet. Her complaints at entry (June 1940) were weakness, fatigue, anorexia, epigastric fulness and distress. The following signs were noted: a large, firm liver, several vascular spiders, increased dye retention, minimal flocculation reaction, normal serum proteins. While in the hospital she was treated with the nutritious diet and vitamin supplements previously described, and after 2 months she was discharged as improved. The liver edge had receded, and vascular spiders had decreased in number. The dye test, however, was still abnormal. She resumed her previous dietary habits, and was seen at irregular intervals in the clinic. One year later (May 1941) the earlier symptoms had reappeared. Tests at this time showed elevated serum globulin, strongly positive flocculation reaction, and increased dye retention. Hospitalization was refused by the patient.

In January, 1942 the patient donated a pint of blood to the Red Cross. Shortly after this her teeth were extracted, and her diet became reduced to alcoholic beverages. In August signs of liver failure developed, including jaundice, massive ascites, palpable liver and spleen, and reduced scrum albumin. She entered the hospital in September. After two months of dietary treatment these signs have partially regressed. Jaundice and ascites have disappeared. Scrum albumin has increased. The patient is ambulatory and she feels well.

This patient, then, exhibited a satisfactory response to treatment when liver damage was slight, relapse on discontinuing therapy, and a second response to treatment after failure set in. It is likely that her liver failure would have been prevented had this patient been conscientious two years ago when changes were minimal.

In general, the changes in this group of patients with symptoms and signs of early liver damage respond readily to the dietary treatment previously described. It is in the treatment of this early stage of liver disease that preventive medicine should be most useful in the future.

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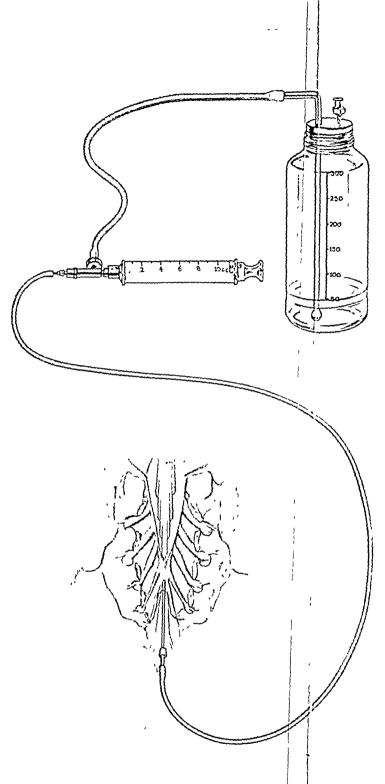
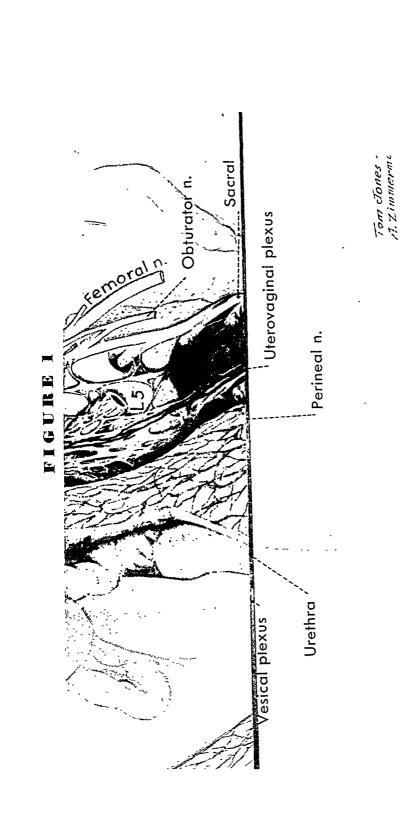


FIGURE 2—Apparatus with needle properly placed in sacral canal.

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THE PRESENT STATUS OF CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS*

Waldo B. Edwards and Robert A. Hingson

Passed Assistant Surgeons, U.S.P.H S

the last edition of Williams' Obstetrics: "If satisfactory analgesia were always possible, drugs having an amnesic action could be entirely dispensed with."

Our experience with Continuous Caudal Analgesia

Our experience with Continuous Caudal Analgesia has presented convincing evidence that labor and delivery does occur with almost perfect comfort for the parturient, without the necessity of any annesic or an anesthetic drug.

Our approach to the problem of safe painless childbirth has followed the application of the principles of regional nerve block to those nervous pathways concerned with the transmission of painful stimuli excited during labor and delivery. While our efforts for several years were directed toward the solution of the problem, we were encouraged by the discussion of this subject by DeLee: 2 "Why put the whole body under anesthesia when you are going to operate on one part? There are three reasons for local and regional anesthesia: first, its availability; second, its safety from complications; and third, the after results."

In adding the continuous feature to the time-honored and established procedure of caudal analgesia, we give full credit to the pioneers, who for four decades have used the method in the several branches of surgery and obstetrics. The single caudal injection was introduced independently and simultaneously by the French surgeons Sicard³ and Cathelin⁴ in the year 1901. Within a short time Cathelin was able to report a thousand cases in which the procedure was used on man, mainly for the relief of bed-wetting. Cathelin envisioned but did not attempt use of the method to alleviate the pains of labor.

The single injection technique of caudal analgesia has been more widely used in surgery than in obstetrics. Läwen⁵ first described such an application in 1910. Others took up the method, finding it well-suited

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for operations by the perineal approach in the fields of urology, proctology and gynecology. By 1920 Zweifel⁶ was able to find 4,200 cases recorded in the literature. In this large series there were ten postoperative deaths. Seven of them seemed obviously independent of the anesthesia; the remaining three occurred respectively a few seconds, seven minutes, and ten minutes after the sacral injection of 0.6 gm. or more of procaine. Six-tenths gram of procaine is now considered a rather large dose for such an injection.

Clinical reports concerning single-injection caudal analgesia in surgery are extremely numerous. Among the earliest American publications are those of Harris⁷ in 1915, and Lewis and Bartels⁸ in 1916 and Thompson⁹ in 1917. Oswald S. Lowsley of New York City reported seventy cases in 1923. John S. Lundy of the Mayo Clinic has reported 15,000 cases without a death. Incidentally, this is the largest series under any single form of anesthesia of that clinic without a fatality. Referring to both caudal and trans-sacral analgesia, he says: "Sacral block is one of the most satisfactory methods available to the anesthetist in the whole field of anesthesia. It is difficult only for those who will not take the trouble to train themselves in the technique."

The first actual application of caudal analgesia to obstetrics was apparently made by Stoeckel of Marburg in 1909. Using procaine, which had not been available to Sicard and Cathelin, he attained a considerable measure of success in relieving the pangs of childbirth in 141 normal cases. With the procedure he was able to distinguish two types of pain during labor, those which we now associate respectively with uterine contractions and with distention of the birth canal. Stoeckel was impressed especially by the great relaxation of the pelvic floor and perineum, the lack of impairment of uterine contractions, and the vigor and well-being of the babies. While acknowledging freely the need for technical improvement in the method, he emphasized its safety and the load of anxiety it lifts from the physician's shoulders in the conduct of labor.

Schlimpert of Leipzig also became interested in the method, and in an address in the United States in 1913¹⁰ reported on its use in approximately fifty cases.

On this side of the Atlantic Meeker and Bonar, 11, 12 Oldham 13, 14, 15 and Rucker 16, 17 seem to have been pioneers in its obstetrical use. Meeker reports specifically on ninety cases, Oldham on more than 500, and

Rucker over one thousand. Since 1930 articles have been published by Cleland, ¹⁸ Baptisti, ¹⁹ Poole, ²⁰ Hopp, ²¹ and Lahmann and Mietus. ²² The largest series in this group is that of Lahmann and Mietus with 400 cases.

For all of these men the only serious disadvantage of the single injection method was its limited duration. It did not suffice for the entire period of labor, and its usefulness in delivery was made uncertain by the unpredictable time of that event. All too often the effect wore off before delivery in primiparae and was induced too late to become fully effective for delivery in multiparae.

The introduction of the continuous feature has eliminated this difficulty. It is now possible to maintain the parturient free of pain from the time labor is definitely established until relief is no longer needed.

In the development of continuous caudal analgesia, it became necessary to find a drug that would prove safe for mother and child while relieving the pains of labor through regional nerve block.

In our search for this drug we used all of the recognized cocaine derivatives and cocaine substitutes in varying concentrations and in different vehicles. In our opinion metycaine most nearly met these criteria. It has the most lasting effect and produces no toxic symptoms.

Our experience confirmed the earlier observations of Ferguson,²³ Lundy,²⁴ Tuohy,²⁵ Fulton,²⁶ Mentzer,²⁷ and Lahmann and Mietus.²² To more than one thousand surgical and obstetrical patients we have administered more than four thousand grams of metycaine without a single toxic reaction in mother or baby that could be attributed to the anesthetic solution. Nor has there been a single case of post-analgesia neuropathy. The patients were under this form of analgesia from one to thirty-three hours for an average of four hours and thirty, minutes. This represents approximately 7.5 mg. of the drug per kilogram of body weight per hour.

It is necessary to multiply this dose by six times before comparable hourly doses in pregnant rabbits will produce signs of toxemia as evidenced by convulsions. It is necessary to multiply this dose by ten times before an appreciable number of feral rabbits will be born dead.²⁸ These studies were carried out on more than fifty pregnant rabbits one and two days before delivery. In most of them hourly doses of the metycaine were given for ten consecutive doses.

Also of fundamental importance in the production of continuous caudal analgesia is the special apparatus consisting of: (a) Graduated

reservoir bottle, (b) Rubber tube and metal sinker, (c) Special automatic two way 470V valve with Luerlok connection, (d) One mm. garter tubing four feet in length, (e) Special malleable, stainless steel needle, (f) Small hose connector for aspiration (Figure 2).

The most important part of the apparatus is the malleable needle. This needle is so constructed that it will assume the curvature of the sacral canal for many hours under considerable stress without breakage and without obliteration of the lumen. The development of this needle has materially lessened the dangers incurred with the ordinary types of steel needles. In our series it has been used more than four hundred times without breakage. However, until experience has been sufficient to test the durability of the needle, we recommend that it be discarded after five complete labors and deliveries.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

A fundamental knowledge of the anatomy of the sacral area and of the nerve supply to the uterus is a prerequisite for success in continuous caudal analgesia. The anatomical proximity of the sacral hiatus to the nerves of the pelvis, perineum and lower extremities makes this method applicable for operative work in these regions.

Centuries ago the Greek anatomists named the large triangular bone at the lower extremity of the vertebral column the "sacred bone" or the sacrum. Since it was the last bone of the body to disintegrate in the grave and since it contained the bony canal into which the animal spirits or the soul of man were supposed to migrate during sleep, it came to have a special emphasis and significance. When we consider that the nerve pathways of locomotion, micturition, defecation, parturition, and reproduction traverse the sacral canal, it is easy for us to understand why the Greeks thought the soul of man was located here.

The peridural space surrounding the dura mater from the foramen magnum to the hiatus sacralis comprises the area between the dura mater and the periosteum lining the spinal canal. The sacral canal is a continuation of the spinal canal, but usually at the second sacral segment communication between these two parts is interrupted by the closure of the dura around the nerve trunks. In dissection of cadavers we found that the dura sometimes encircles the spinal nerves of the cauda equina and the filum terminale all the way to the fourth or fifth sacral segment. In these instances spinal fluid can be obtained by inserting a short needle

into the sacral hiatus. This phenomenon has been observed by us only three times in 1,000 caudal injections. The occurrence of anomalies and malformations of the vertebral and spinal canals should be kept in mind continuously.

Upon the outer surface of the dura, in the epidural space, especially at the sides are extensive venous plexuses and loose adipose tissue.

The sacral canal terminates below in the hiatus sacralis, forming a triangular opening, the sides of which are marked by the bony ridges known as the sacral cornua. This opening varies in size and shape in different individuals. It may be abnormally large, owing to a deficiency in one or more of the vertebral arches, or it may be reduced to the extent of bony obliteration (Figure 3). These sacral specimens were obtained in the department of anatomy of the Jefferson University Medical School in Philadelphia.

In working in the necropsy material in the same laboratory in conjunction with Doctors Vaux and Lull we found that when 30 cc. of solution was injected into the peridural space, the uppermost extent of the dye was the sixth dorsal segment. In all of them the dye extended on both sides as high as the tenth dorsal segment. This is exactly the picture we have been able to produce on the living parturient. Therefore our initial dose is 30 cc. of one and one-half per cent metycaine, and in the majority of the patients there will be an analgesia produced as high as the line midway between the pubis and the umbilicus. We have found that whenever such a level of analgesia is attained, the pains of labor are relieved.

NERVE SUPPLY TO THE UTERUS

In 1893 Head, the English physiologist, postulated that the sensory nerve supply to the uterus was located in the fibers of the sympathetic nervous system in the region of the lower dorsal segments. Cleland¹⁸ in 1933 more accurately located these pathways as coursing through the sympathetic ganglia of the eleventh and twelfth dorsal segments.

Our work has substantiated these contentions. At the present time we believe that the nerve supply to the uterus is divided into three separate anatomical components. These we have attempted to show in the lantern slide of the anatomical drawing done for us by Tom Jones (Figure 1).

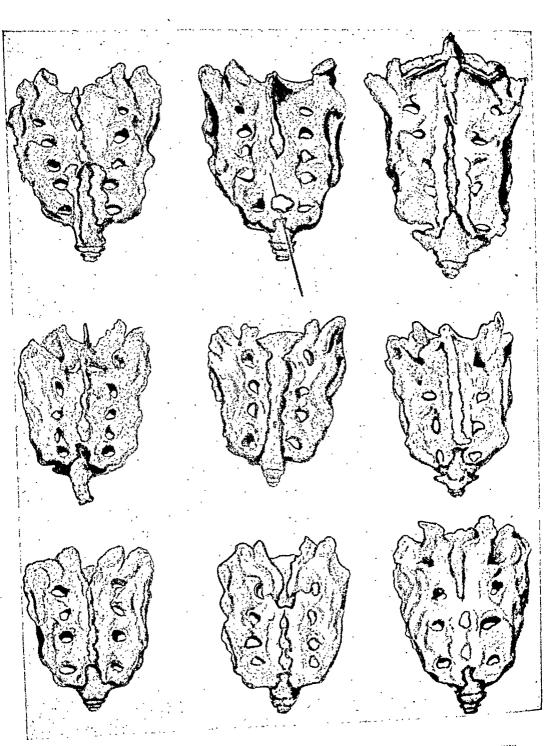


Figure 3: Sacral specimens, showing variations in the anatomy of the human sacrum.

ABSOLUTE ANESTHETIC CONTRAINDICATIONS

1. Local infection at the site of the area to be injected, such as a furuncle or a pilonidal cyst.

2. A low lying dura mater, as determined by an aspiration of spinal fluid. This is an absolute contraindication. In such a case the needle is to be withdrawn and the case handled in some other way.

3. Deformity of the sacrum with bony obliteration of the sacral hiatus. This condition is extremely rare. It occurs perhaps less than one time in 500 cases.

4. A history of sensitivity to the drug.

RELATIVE CONTRAINDICATIONS

- 1. The unusually obese individual in whom the sacral hiatus cannot be palpated. Already in three clinics we have seen beginners with the technique insert the needle and after several minutes declare the method was no good for these particular cases. Rectal examinations revealed the presence of the needle anterior to the sacrum and in two cases through the wall of the rectum. We would like to emphasize that blind prodding with a needle is not good anesthesia nor safe obstetrics.
- 2. The hysterical patient would also be a poor candidate for this regime.
- 3. Repeated aspirations of blood through the caudal needle indicating that the needle is in a vein or a capillary plexus. The skilled anesthetist knows how to manipulate the needle outside of such a site and then continue with the injection. The beginner will learn only through special training.

COMPLICATIONS

We hope that by emphasizing our complications, the medical men who use this method after us will avoid some of our mistakes and our difficulties.

- of our series when we were using different types of needles, was breakage of the needle at the hub. After twelve such experiences in four of which we had to make surgical incisions, we have eliminated this flaw by perfection of a malleable stainless steel needle.
 - 2. Infection. In our series of more than one thousand obstetric and

surgical continuous caudal analgesias, there has been only one infection. This was an obstetrical case which developed a peridural abscess with Staphylococcus aureus and a bacteriemia uncontrolled by rigid sulfonamide therapy. This patient died on the thirty-first day after delivery.

In analyzing the portal of entry of the infection three sources must be kept in mind:

- 1. The skin of the patient through which the needle was inserted.
- 2. The injected solution.
- 3. Some break in technique on the part of the operator in making subsequent injections. We are working at the present time on perfecting a syringe whereby contamination by the operator will be impossible.

We have had a few minor systemic complaints which we have been able to remedy with slight modifications of technique and management. These have been slight, temporary headache at the time of initial injection in an occasional case; back-ache between the shoulders when the parturient spends too much time on her back; a feeling of an ache or pressure along the course of the sciatic nerve as the solution is injected.

Besides the complications listed, our patients have had comfortable labors and deliveries.

The technique of administration is one that must be learned by actual experience. We consider that more than 80 per cent of the injections are easier than lumbar puncture. An initial injection of 30 cc. of metycaine solution and subsequent injections of 20 cc. every forty minutes to one hour will keep the average obstetrical case comfortable.

The key-hole whereby the entire problem of pain in childbirth may be unlocked is the sacral hiatus. The malleable caudal needle is the key. The adequate dosage of metycaine necessary to block the pathways of pain involved in parturition is the combination of that lock.

After managing the obstetrical labors and deliveries of 660 cases with only one maternal fatality and the deliveries of 654 live babies, we are convinced that in the hands of doctors specially trained, painless childbirth can be managed by continuous caudal analgesia in the overwhelming majority of all hospital patients. One-fourth of these deliveries were carried out in our own hospital; one-fourth of them were carried out in the Philadelphia-Lying-In and Jefferson University Hospitals under the direction of Dr. Norris Vaux and Dr. Clifford Lull. The other half were accomplished in recognized obstetrical teaching

hospitals associated with twenty-three medical schools under the direction of the members of the American Society of Obstetricians, Gynecologists and Abdominal Surgeons, where we appeared in the United States and Canada on invitation for purposes of demonstration and lecture.

The interpretation of the obstetrical findings and the management of the cases from this standpoint will now be discussed by Doctor Edwards.

DeLee said: "It is the duty of the obstetrician to mitigate the sufferings of natural labor."

The amnesics to screen painful memories, the hypnotics to promote sleep, the anesthetics to block out all central perception have all been used with varying degrees of satisfaction to patient and obstetrician. Caudal block with a single injection is useful but produces analgesia for only a limited period. We believe that continuous caudal analgesia will be an addition to the obstetrician's armamentarium. In our hands it has had no bad effect on either mother or child and has been successful in making labor and delivery painless.

We believe it to have the following advantages:

- 1. There is freedom from pain beginning five to fifteen minutes after the first injection and this painless state can be maintained as long as necessary, by repeated injections.
- 2. Consciousness and motor function on the part of the mother are not impaired.
- 3. There is no interference with the rate and strength of uterine contractions.
- 4. The respiratory and other vital mechanisms of the child are not obtunded.
- 5. The duration of labor has been shortened in the majority of our cases.
 - 6. The management of unfavorable fetal positions is facilitated.
 - -. Postpartum hemorrhage is minimized.
- 8. The incidence and severity of maternal postpartum complications are reduced.
- 9. There has been no observed adverse effect in the course of cardiac or pulmonary disease in our few observed cases.
- 10. Patients having metabolic diseases necessitating special feeding can continue their diet while under caudal anesthesia.

The course of labor under continuous caudal analgesia presents some points of difference.

Cervical dilatation is usually rapid in both primipara and multipara, and the first stage of labor is materially shortened, an effect apparently due largely to cervical and perineal relaxation. Likewise, the early part of the second stage is expedited. The later part of the second stage is definitely prolonged, since uterine contractions alone are seldom adequate for the final delivery. Thus, precipitation is rarely seen. Because she is unaware of her uterine contractions the patient lacks any compulsion to strain. The parturient is, however, able to add the expulsive power of her abdominal musculature and diaphragm to that of uterine contractions and spontaneous delivery is not difficult.

The cervix and perineal tissues are so completely relaxed that outlet forceps and episiotomy, if necessary, are relatively simple procedures. The lack of expulsive desire is in many ways an advantage to the accoucheur, since the patient is able to coöperate fully in giving him complete control of the progress of the head over the perineum.

Especial care is necessary to clear the respiratory passage of the infant at the first possible opportunity, for the babies are usually ready to breathe the instant their noses cross the perineum. This quick onset of spontaneous respiration is one of the striking and consistent observations in babies delivered under caudal. Thus we have no resuscitation problem.

The rapid and normal separation and expulsion of the placenta from the uterus without the administration of oxytocics has been almost without exception in our experience. The average measured blood loss has been from 40 to 90 cc. Often the loss from the episiotomy exceeds in volume that from the uterus. Postpartum complications are conspicuously absent. In only one case was there a retention of the placenta and this was a cornual implantation that was extracted manually. The average duration of labor from the inception of analgesia has been six hours. Of the patients 80 per cent were primiparae and analgesia was usually begun as soon as the onset of labor could be definitely ascertained.

During the course of labor and immediately after delivery, the patients may be given a regular diet, since the method does not interfere with gastrointestinal function.

Continuous caudal analgesia should be used to relieve pain. If the parturient is not in actual need of relief there is obviously no indication for its use. It should be started only when labor has definitely begun.

Ideally the expectant mother should be having hard pains at two to three minute intervals with effacement of the lower uterine segment and one to two cms. cervical dilatation.

This method will not be entirely satisfactory in the neurotic subject. Placenta praevia and marked disproportion between the child and the birth canal, are definite contraindications. In placenta praevia there may be severe hemorrhage because of cervical relaxation. This analgesic agent will not relax a contracted pelvis.

The mechanics of delivery can be carried out according to the preference of the obstetrician. We do not advocate that any individual change his method. At no time should he become the slave of the method, but he should keep the method his slave. However, it will soon be noted that extreme relaxation of the cervix and perineum are features of continuous caudal analgesia which greatly facilitate the handling of abnormal presentations, including occiput posterior, transverse arrest and breech presentations.

Dr. Hingson and I want to point out that we have modified caudal analgesia so that it may be employed for as long a period as desired. We have, with help from an instrument manufacturer, secured a better needle and a satisfactory apparatus. With these changes we have applied the method in obstetrics. It is, we hope and believe, a worthwhile addition to pain relieving procedures during childbirth. We present it to you, not as the final word on the subject, but for your evaluation, trial and report. We would reëmphasize that the method is best performed by a specialist, in a hospital.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

February 4-The New York Academy of Executive session-Reading Medicine. of the minutes. ¶ Papers of the evening, scientific program in cooperation with the Section of Medicine and the Section of Surgery-al Is essential hypertension of renal origin? Irvine H. Page, Director of Clinic Research, Lilly Clinic, Indianapolis City Hospital; Homer W. Smith, Professor of Physiology, New York University, College of Medicine; b] Value of surgery in the treatment of hypertension, R. H. Smithwick, Instructor in Surgery, Harvard Medical School. Report on election of Fellows.

February 18—The Harvey Society in affil-

iation with The New York Academy of Medicine. The Fifth Harvey Lecture, "Some Internal Factors Limiting Growths," William J. Robbins, director, New York Botanical Gardens.

SECTION MEETINGS

FEBRUARY 2—Dermatology and Syphilology

¶Presentation of cases—a] Cases from
the Mount Sinai Hospital; b] Miscellaneous cases. ¶ Discussion. ¶ Executive
session.

February 4—Surgery—The Section of Surgery combined its scientific program with the Stated Meeting.

February 9-Combined meeting of Neurologn and Psychiatry and the New York Neurological Society. ¶ Papers of the evening-al The neural mechanism of paralysis agitans, Roland M. Klemme (by invitation); b) Modification of spastic hemiplegia by cortical excision. defferson Browder; Discussion, Tracy J. Putnam, Samuel Brock, Charles Davison; e] Endopsychic factors in the causation of traumatic neuroses, Sandor Lorand; dl Psychiatric reactions to the war as seen in civilians and soldiers referred to a mental hospital. Curtis T. Prout-Discussion, A. A. Brill, Ernst Kris (by invitation). ¶ Exccutive session of the Section.

Fennyary 15—Pediatrics—The Section held a combined meeting with the New York Roentgen Society.

February 15-Ophthalmology. TExecutive session, reading of the minutes. ¶ Papers of the evening-al Some observations on visual functions in strephosymbolics, Samuel T. Orton. General discussion. Chronic orbital myositis, H. Dunnington, R. N. Berke (by invitation). Discussion-John McGavic (by invitation); cl The relationship between intraocular and intracranial hemorrhage in rupture of anenrysm of the cirele of Willis, James N. Greear, Jr. (by invitation). Discussion - Algernon B. Recse; d] Recession of the inferior oblique, James W. White. Discussion-John H. Dunnington, L. W. Hughes (by invitation); e] Epidemic keratoconjunctivitis, Murray Sanders. Discussion -Allson Braley (by invitation).

Medicine—The Section did not hold its regular meeting on February 16, as it combined its scientific program with that of the Stated Meeting on February 4.

Genito-Urinary Surgery—The Section held no meeting in February.

FEBRUARY 17-Otolaryngology-Reading of

the minutes. ¶ Papers of the evening—a] I. A few details and technical hints in rhinoplasty. 2. Operation for traumatic deformity of the nose and forehead (colored motion picture), Gustave Aufricht; b] Reconstruction of the external ear, Jerome Pierce Webster; c] New techniques in rhinoplastic surgery (Moving picture and slide demonstration), John A. Cinelli (by invitation), Gerhard H. Cox (by invitation), Vilray P. Blair, St. Louis, Missouri. ¶ General discussion. ¶ Executive session.

Fennuary 19—Orthopedic Surgery. ¶ Reading of the minutes. ¶ Papers of the evening—a] The occurrence of scoliosis in anterior poliomyelitis, Frederick vom Saal (by invitation); b] A critical analysis of the management of paralytic scoliosis, Samuel Kleinberg; c] The endresults of correction and maintenance by surgical fixation, John Cobb. Discussion—Alan DeForest Smith. ¶ General discussion. ¶ Executive session.

February 23-Obstetrics and Gynecology. ¶ Executive session, reading of the minutes. ¶ Case reports, Streptococcus viridans pneumonia (prepartum and intrapartum) and pulmonary embolism (postpartum) with recovery, Haig Carapaytan (by invitation). ¶ Papers of the evening-a] The value of pelvioradiography in the management of dystocia, Arthur Weinberg (by invitation), Samuel J. Scadron; b] Continuous caudal analgesia in obstetrics, Robert A. Hingson (by invitation), Waldo B. Edwards (by invitation). | General discussion.

AFFILIATED SOCIETIES

February 15—Combined Meeting of New York Roentgen Society and the Section of Pediatrics. ¶ Reading of the minutes. ¶ Papers of the evening: Tuberculosis in adolescents—a Pathogenesis and clinical picture, Edith M. Lincoln; b] Treatment and prognosis, J. Burns Amberson, Jr. Discussion—Herbert R. Edwards, Max Pinner, Lewis J. Friedman (by invitation).

February 25-New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Papers of the evening-a] Acute ulceration of the esophagus with associated intranuclear inclusion bodies, John M. Pearce; bl Malignant tumors of peripheral nerves. Arthur Purdy Stout (by invitation); cl Pathological findings in unexpected deaths in infancy and childhood, Jacob Werne. Executive session.

CALDWELL, WILLIAM EDGAR: 875 Park Avenue, New York City; born in Northfield, Ohio, February 23, 1880; died in New York City, April 1, 1943; graduated in medicine from New York University and Bellevue Hospital Medical College in 1904; elected a Fellow of the Academy January 3, 1918.

Dr. Caldwell was instructor and afterward assistant professor of obstetrics at New York University, 1908-19; associate professor of obstetrics and gynecology at the College of Physicians and Surgeons, Columbia University, 1919-27, when he was promoted to professor of clinical obstetrics and gynecology; consulting obstetrician and gynecologist to Presbyterian Hospital, New Rochelle Hospital and Monmouth Memorial Hospital; and associate director of Sloane Hospital for Women. He was a Fellow of the American College of Surgeons, the American Medical Association, a diplomate of the American Board of Obstetrics and Gynecology, and a member of the American Gynecological Society and the State and County Medical Societies.

DYKE, CORNELIUS GYSBERT: 706 West 168 Street, New York City; born in Orange City, Iowa, July 25, 1900: died in New York City, April 23, 1943; graduated in medicine from the State University of Iowa in 1926; elected a Fellow of the Academy November 7, 1935, and served the Academy as a member of the Committee on Admission from 1942 until his death.

Dr. Dyke was associate professor of radiology at the College of Physicians and Surgeons, Columbia University; attending radiologist to the Presbyterian Hospital; and director of radiology at the Neurological Institute. He was a Fellow of the American Medical Association, a diplomate of the American Board of Radiology, and a member of the American Neurological Association, the American Roentgen Ray Society, the American College of Radiology, the Harvey Cushing Society, and the State and County Medical Societies.

HABERMAN, JULES VICTOR: 156 West 86 Street, New York City; born in New York City, April 11, 1878; died April 9, 1943; received the degree of B.A. from Columbia University in 1902 and graduated in medicine from the College of Physicians and Surgeons in 1905; elected a Fellow of the Academy October 7, 1909.

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



AUGUST, 1943

OLIVER WENDELL HOLMES

A Century's Vindication of His Work on Puerperal Fever*

B. P. Watson

Director of Sloane Heer tal fer Wemen

man who just one hundred years ago wrote and published an Essay which is unique in medical literature. It is at once a model of cold scientific reasoning and of find in it a statement which is false or an argument which can be refuted; and we still need to take to heart his plea that, through ignorance or prejudice, we do not fail to use every means which will make childbearing safer for women throughout the world.

There has been so much controversy in the past as to who first proved the contagiousness of puerperal fever and laid down rules for combating it, that a statement of the facts seems appropriate to this occasion. The more so that Holmes never made any such claim for himself, and would have been outraged had it been made on his behalf.

When in 1843 he wrote his Essay entitled "The Contagiousness of Puerperal Fever" Holmes was a young man of thirty-four years of age. He had obtained his M.D. degree in the Harvard Medical School just

^{*} Read February 19, 1943 at The New York Academy of Medicine in the Centenary Celebration of the publication by Oliver Wendell Holmes of his paper on The Contaguousness of Puerfeed Lever.

seven years before and in the interval had been for two years professor of anatomy and physiology in Dartmouth College.

In 1840 he returned to Boston and in 1847 was appointed Parkman Professor of Anatomy and Physiology in Harvard Medical School. There is no evidence that he ever practiced obstetrics and he never mentions that he ever treated a case of puerperal fever himself but doubtless he saw cases during a two year sojourn in Paris, where it was rampant in the hospitals.

Here then is a remarkable fact that the Essay, which for us has become a classic, was written by a man who had no practical experience of the subject with which it deals.

How he came to write it he tells in the preface to a monograph entitled "Puerperal Fever as a Private Pestilence" published in 1855. In this booklet the original Essay is reproduced together with additional facts and with replies to his various critics. These are his words:

"It happened, some years ago, that a discussion arose in a Medical Society, of which I was a member, involving the subject of a certain supposed cause of disease, about which something was known, a good deal suspected, and not a little feared. The discussion was suggested by a case, reported at the preceding meeting, of a physician who made an examination of the body of a patient who had died with puerperal fever, and who himself died in less than a week, apparently in consequence of a wound received at the examination, having attended several women in confinement in the mean time, all of whom, as alleged, were attacked with puerperal fever.

"Whatever apprehensions and beliefs were entertained, it was plain that a fuller knowledge of the facts relating to the subject would be acceptable to all present. I, therefore, felt that it would be doing a good service to look into the best records I could find, and inquire of the most trustworthy practitioners I knew, to learn what experience had to teach in the matter, and arrived at the results contained in the following pages:

"The Essay was read before the Boston Society for Medical Improvement, and at the request of the Society, printed in the New England Quarterly Journal of Medicine and Surgery, for April, 1843. As this Journal never obtained a large circulation and ceased to be published after a year's existence, and as the few copies I had struck off separately were soon lost sight of among the friends to whom they were

sent, the Essay can hardly be said to have been fully brought before the Profession.

"The subject of this Paper has the same profound interest for me at the present moment, as when I was first collecting the terrible evidence out of which, as it seems to me, the commonest exercise of reason could not help shaping the truth it involved. It is not merely on account of the bearing the question,—if there is a question,—on all that is most sacred in human life and happiness, that the subject cannot lose its interest. It is because I most fully believe that a fair statement of the facts must produce its proper influence on a very large proportion of well constituted and unprejudiced minds. Individuals may, here and there, resist the practical bearing of the evidence on their own feelings or interests; some may fail to see its meaning, as some persons may be found who cannot tell red from green; but I cannot doubt that most readers will be satisfied and convinced, to loathing, long before they have finished the dark obituary calendar laid before them.

"I do not know that I shall ever again have so good an opportunity of being useful as was granted me by the raising of the question which produced this Essay. For I have abundant evidence that it has made many practitioners more cautious in their relations with puerperal females, and I have no doubt it will do so still, if it has a chance of being read, though it should call out a hundred counterblasts, proving to the satisfaction of their authors that it proved nothing. And, for my own part, I had rather rescue one mother from being poisoned by her attendant, than claim to have saved forty out of fifty patients, to whom I had carried the disease. Thus, I am willing to avail myself of any hint coming from without, to offer this paper once more to the press. The occasion has presented itself, as will be seen, in a convenient, if not in a flattering form . . . I send this Essay again to the Medical Profession, without the change of a word or syllable."

The Essay itself begins as follows: "In collecting, enforcing and adding to the evidence accumulated upon this most serious subject, I would not be understood to imply that there exists a doubt in the mind of any well-informed member of the medical profession as to the fact that puerperal fever is sometimes communicated from one person to another, both directly and indirectly.

"It signifies nothing that wise and experienced practitioners have sometimes doubted the reality of the danger in question; no man has the right to doubt it any longer. No negative facts, no opposing opinions, be they what they may or whose they may, can form any answer to the series of cases now within the reach of all who choose to explore the records of medical science."

What he does in his Essay is to marshal these records from the medical literature to drive home the point he wishes to make, viz., that "The disease known as Puerperal Fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses." In reviewing the literature he gives every possible credit to the real pioneers. The first he mentions is Dr. Alexander Gordon of Aberdeen, Scotland, who in 1795 had published in London a book entitled: "A Treatise on the Epidemic Puerperal Fever of Aberdeen." In this work, Gordon, from a review of seventy-seven (77) cases-in which he traced the channel of propagation-came to the conclusion "that every person who had been with a patient in the puerperal fever became charged with an atmosphere of infection, which was communicated to every pregnant woman who happened to come within its sphere. This is not an assertion, but a fact, admitting of demonstration. . . . It is a disagreeable declaration for me to mention that I myself was the means of carrying the infection to a great number of women." He states further "I arrived at that certainty in the matter, that I could venture to foretell what woman would be affected with the disease, upon hearing by what midwife they were to be delivered, or by what nurse they were to be attended during their lying-in: and, almost in every instance, my prediction was verified."

Holmes devotes only one short paragraph to Dr. Charles White of Manchester. He was the first to make a real contribution to the understanding and prophylaxis of the disease. His work entitled "A Treatise on the Management of Pregnant and Lying-In Women and the Means of Curing, but More Especially of Preventing the Principal Disorders to Which They Are Liable," was published in London in the year 1773.

White attributed as the chief causes of puerperal fever, bad air, filthy bedding, and the retention of secretions in the uterus and vagina. He emphasized the need of ventilation, clean rooms, clean linen, the isolation of patients in separate rooms in hospitals, and the immediate removal of patients with the disease from those unaffected. After a patient with fever left the room all bedding and curtains were to be washed, and the floor and woodwork cleansed with vinegar. His teach-

ing became generally known all over Britain, and, before the close of the Century, it was recognized by many that the disease might be conveyed by the attendant from one patient to another.

This teaching bore immediate fruit, as shown by the results obtained in the Rotunda Hospital, Dublin, under the Mastership of Robert Collins who, in the report covering his Mastership, from 1826 to 1833, tells how, from the time he carried out a thorough cleaning of the wards, using copiously on the floors and wood work chloride of lime, he abolished childbed fever altogether, although in the immediately preceding years, there had been extensive outbreaks. He wrote "From this time (i. e., since he adopted the methods of White) until the termination of my Mastership in November, 1833, we did not lose one patient by this disease. As the Wards of the Hospital are occupied by the patients in rotation, as soon as each in succession was vacated I continued the use of the chloride of lime, confining its application to the floors. In this way each Ward was washed every ten or twelve days. the solution being left undisturbed for twenty-four hours, during which time the blankets, quilts, linen, etc., were suspended, so as to be exposed completely to the chlorine gas, which is copiously disengaged from the preparation mentioned."

White's teaching also found its way to the Continent of Europe, and Boer introduced White's methods into the Allgemeines Krankenhaus in Vienna in 1789, with the result that he reduced the mortality over a period of thirty years to 1.3 per cent. Both before and after his time it was appallingly high, sometimes reaching to 20 per cent. In France, White's methods did not receive the same recognition, the prevalent view being that puerperal fever was a specific miasmatic disease. It was not until the time of Tarnier that opinion definitely changed, and it was only in 1876 that there was erected, according to Tarnier's plans, a pavilion in the grounds of the Maternité de Paris which provided separate rooms for each patient (Couvelaire).

Holmes was conversant with all that White wrote and of the good results which followed the observance of his rules for the prevention of the disease in hospitals. He was, however, more concerned in driving home the facts proving its conveyance from person to person in ordinary practice. So after quoting White briefly he goes on to cite instances recorded in more recent English literature where puerperal fever followed the trail of certan practitioners and midwives whilst it

did not occur in the practice of others in the same neighborhood. He sums up this part of his presentation as follows:

"The recurrence of long series of cases like those I have cited, reported by those most interested to disbelieve in contagion, scattered along through an interval of half a century, might have been thought sufficient to satisfy the minds of all inquirers that here was something more than a singular coincidence. But if on a more extended observation, it should be found that the same ominous groups of cases, clustering about individual practitioners, were observed in a remote country, at different times, and in widely separated regions, it would seem incredible that any should be found too prejudiced or indolent to accept the solemn truth knelled into their ears by the funeral bells from both sides of the ocean—the plain conclusion that the physician and the disease entered, hand in hand, into the chamber of the unsuspecting patient.

"That each series of cases have been observed in this country and in this neighborhood, I proceed to show."

He then quotes from published articles in American journals and from personal letters from general practitioners and obstetricians in the Boston area, all testifying to the fact that deaths from puerperal fever occurred in series in the practice of those who had attended cases of erysipelas, had performed autopsies on women dying of puerperal fever, or had attended them in their illness.

His whole argument is built up in the most perfect forensic style with cases cited and authorities quoted. And then he lets himself go in an appeal to the profession. No advocate pleading the cause of an innocent defendant before a hostile jury could be more eloquent. I quote: "I have no wish to express any harsh feeling with regard to the painful subject that has come before us. If there are any so far excited by the story of these dreadful events, that they ask for some word of indignant remonstrance, to show that science does not turn the hearts of its followers into ice or stone, let me remind them that such words have been uttered by those who speak with an authority I could not claim. It is as a lesson rather than as a reproach that I call up the memory of these irreparable errors and wrongs. No tongue can tell the heartbreaking calamity they have caused; they have closed the eyes just opened upon a new world of love and happiness; they have bowed the strength of manhood into the dust; they have cast the helplessness of infancy into the stranger's arms, or bequeathed it with less cruelty the death of its

dying parent. There is no tone deep enough for regret, and no voice loud enough for warning. The woman about to become a mother, or with her new-born infant upon her bosom, should be the object of trembling care and sympathy wherever she bears her tender burden, or stretches her aching limbs. The very outcast of the streets has pity upon her sister in degradation when the seal of promised maternity is impressed upon her. The remorseless vengeance of the law, brought down upon its victim by a machinery as sure as destiny, is arrested in its fall at a word which reveals her transient claim for mercy. The solemn prayer of the liturgy singles out her sorrows from the multiplied trials of life, to plead for her in her hour of peril. God forbid that any member of the profession to which she trusts her life, doubly precious at that eventful period, should hazard it negligently, unadvisedly, or selfishly!"

Then returning to a cold appraisal of the subject he says: "There may be some among those whom I address, who are disposed to ask the question, What course are we to follow in relation to this matter? The facts are before them, and the answer must be left to their own judgment and conscience. If any should care to know my own conclusions, they are the following; and in taking the liberty to state them very freely and broadly, I would ask the inquirer to examine them as freely in the light of the evidence which has been laid before him.

- 1. A physician holding himself in readiness to attend cases of midwifery, should never take any active part in the post-mortem examination of cases of puerperal fever.
- 2. If a physician is present at such autopsies, he should use thorough ablution, change every article of dress, and allow twenty-four hours or more to elapse before attending to any case of midwifery. It may be well to extend the same caution to cases of simple peritonitis.
- 3. Similar precautions should be taken after the autopsy or surgical treatment of cases of erysipelas, if the physician is obliged to unite such offices with his obstetrical duties, which is in the highest degree inexpedient.
- 4. On the occurrence of a single case of puerperal fever in his practice the physician is bound to consider the next female he attends in labor, unless some weeks, at least, have elapsed, as in danger of being infected by him, and it is his duty to take every precaution to diminish her risk of disease and death.

- 5. If within a short period two cases of puerperal fever happen close to each other, in the practice of the same physician, the disease not existing or prevailing in the neighborhood, he would do wisely to relinquish his obstetrical practice for at least one month, and endeavor to free himself by every available means from any noxious influence he may carry about with him.
- 6. The occurrence of three or more closely connected cases, in the practice of one individual, no others existing in the neighborhood, and no other sufficient cause being alleged for the coincidence, is prima facie evidence that he is the vehicle of contagion.
- 7. It is the duty of the physician to take every precaution that the disease shall not be introduced by nurses or other assistants, by making proper inquiries concerning them, and giving timely warning of every suspected source of danger.
- 8. Whatever indulgence may be granted to those who have here-tofore been the ignorant causes of so much misery, the time has come when the existence of a private pestilence in the sphere of a single physician should be looked upon not as a misfortune but a crime; and in the knowledge of such occurrences, the duties of the practitioner to his profession, should give way to his paramount obligations to society."

All this was written in the year 1843 and his conclusions are as valid today, one hundred years later, as they were then. I do not suppose there is a physician in the world today who does not know and honor the name of Oliver Wendell Holmes, but many of his contemporaries upbraided him bitterly for casting what they regarded as aspersions on members of the medical profession. One of his most bitter opponents was Charles D. Meigs, Professor of Midwifery and the Diseases of Women and Children in Jefferson Medical College, Philadelphia—the same Professor Meigs who later opposed equally vehemently the use of anesthesia in obstetrics as introduced and advocated by James Young Simpson. Meigs was supported by his fellow townsman, Hugh L. Hodge, Professor of Obstetrics in the University of Pennsylvania. Holmes answered the criticism of these and other opponents in very effective fashion when he re-published the Essay in 1855, but they still remain unconvinced. Of them he says:

"The teachings of the two Professors in the great schools of Philadelphia are sure to be listened to, not only by their immediate pupils. but by the Profession at large. I am too much in earnest for either humility or vanity, but I do entreat those who hold the keys of life and death, to listen to me also this once. I ask no personal favor; but I beg to be heard, in behalf of the women whose lives are at stake, until some stronger voice shall plead for them. . . . Let it be remembered that persons are nothing in this matter; better that twenty pamphleteers should be silenced, or as many professors unseated, than that one mother's life should be taken."

Holmes, although a professor himself, hadn't any great respect for professors as such. In his address on the occasion of the rooth Anniversary of the founding of the Medical School of Harvard University in 1883 he described some of those he had encountered in Paris in his early years as follows: "Two or three water-logged old professors were moored to their chairs; one of them not so very old, but with a good many ancient barnacles about him; one formidable three decker. Broussais, with his upper tier of guns still above the water-line and banging away at the assailants of his famous 'physiological doctrine'."

There was one professor among his contemporaries who supported Holmes through thick and thin, and that was Walter Channing, first Professor of Obstetrics in Harvard University. Holmes honored him as a man "vivacious, full of anecdote, ready to make trial of new remedies with the open and receptive intelligence belonging to his name as a birthright." In contrast to Meigs, Channing was the great champion in this country of Simpson's plea for general anesthesia in labor.

Holmes must have felt about criticism what Pasteur said at the conclusion of his Essay on the Germ Theory of Disease read before the French Academy of Sciences in 1880: "I desire judgment and criticism upon all my contributions. Little tolerant of frivolous or prejudiced contradictors, contemptuous of that ignorant criticism which doubts on principle, I welcome with open arms the militant attack which has a method in doubting and whose rule of conduct has the motto 'more light'."

Looking back over one hundred years the blind and prejudiced opposition to the views set forth by Holmes seems outrageous, but do not let us be too sanctimonious in our condemnation. The factual findings of the Committee, appointed by this Academy of Medicine to inquire into maternal mortality in this city, received none too warm a reception from some of the profession when they were published in 1933. It is only human to resent any implication that we who are car-

ing for patients may ourselves be responsible for some of the complications and disasters that may overtake them in the course of our ministrations. I suppose it was for that reason that, in its wisdom, the Academy appointed Dr. Ransom Hooker, a general surgeon, to head that particular Committee. Like Holmes he had never practiced obstetrics and could be absolutely objective in his viewpoint. That the facts were well founded was shown by the unanimity with which the conclusions were accepted within a very short time of their first impact upon an astonished profession.

And now let us try to follow the course of events after the publication of Holmes' Essay. Semmelweis, who almost certainly had never heard of Holmes and who, apparently, was not acquainted with the English or American literature on puerperal fever of the preceding sixty years, published in 1847 the results of his investigations. His work extended over several years, and was characterized by the most painstaking scientific accuracy. He began by noting that, while the mortality was 2.7 per cent in the Wards of the Hospital where nurses only were in attendance, it was as high as 11.4 per cent in those to which doctors and students were attached. He further noted that the mortality among patients treated in their own homes was much lower than that among hospital patients. He then found that the appearances in a subject dying from septicemia, as the result of an autopsy wound, were exactly the same as those present in women dying from puerperal fever. He came to the conclusion that puerperal fever was due to the introduction of cadaveric material into puerperal wounds and that the preponderance of cases among patients attended by students and doctors was due to their artendance in the dissecting room and at autopsies. Acting on this theory he insisted on careful washing of the hands and the use of a solution of chloride of lime, as advocated years before by Charles White.

In 1869 James Young Simpson wrote numerous papers on surgical fever, pointing out the same facs that Semmelweis had noted with regard to the high mortality among Hospital patients as compared with those confined at home. Writing on the planning of Hospitals, in relation to the incidence of Surgical Sepsis, he said "To what extent are Hospitals, as in general, at present constituted—banes or blessings? And how can they be changed so as to convert them from the former to the latter?" He concluded by suggesting that "they should be altered from Wards into rooms, from stately mansions into simple cottages,

from stone and marble palaces into wooden, brick, and iron villages." In one of his lectures he demonstrated the identity in the clinical course, and the autopsy findings of surgical and puerperal fever, and ascribed both to contagion carried by the hands or person of the operator. This was the most convincing exposition, given up till then of the identity of the two conditions, although White in his writings shows that he believed them of the same nature, and Oliver Wendell Holmes and Semmelweis had the same idea.

The teaching of Charles White in England, of Holmes in America, of Semmelweis in Austria, and of Simpson in Scotland was, for the most part, forgotten in the succeeding years.

Whilst Semmelweis was right in his contention that puerperal fevers were the result of inoculation into puerperal wounds of decomposed animal organic matter, either from the dead body or from a living person affected with a disease which produced decomposed animal organic matter, it remained for Pasteur to demonstrate years later that decomposition and putrefaction were due to living organisms, and for Lister to show that it was these organisms, and not the organic matter itself, which were the cause of inflammation and septic fever.

As early as 1863 Mayerhofer demonstrated microörganisms in the lochia of puerperal women, but the nature of these was not recognized. In 1868 Coze and Feltz at Strasbourg found in the blood of a patient with puerperal fever "de nombreux points mobiles isolés ou disposés en chainettes." This was the first demonstration of organisms in the blood of a living patient. Recklinghausen, Waldeyer and Orth in 1872 and 1873 found organisms arranged in chain in the uterus and in the serous exudates of women dying of puerperal fever. These organisms were never cultured, and no animal inoculations were made, so that the pathogenicity of the organisms was not proved. The proof of the causal relationship between these organisms and puerperal fever was furnished by Pasteur himself. Beginning to work on the subject in 1875 with Joubert, Chamberland, and Roux, and later with Doléris, he declared to the Academy of Medicine of Paris in 1879 his conviction that these organisms were the cause of puerperal fever. A few days after his communication he demonstrated in the lochia of a patient dying of puerperal sepsis numbers of organisms, and among them preponderance of those in the "forme de petits chapelets de grains sphériques." He cultured the same organisms in pure culture from the blood of the patient during life and after death, and found them, along with others, in the uterus, tubes, and lymphatics of the pelvis. "Les petits chapelets de grains sphériques" were streptococci (Couvelaire).

Chaveau in 1882 and Arloing in 1884, by inoculation into rabbits of organisms obtained from cases of puerperal sepsis, produced different forms of septic infection, thus absolutely proving the pathogenicity of the streptococci and the identity of puerperal and of surgical sepsis. Knowing nothing of the streptococcus Holmes was convinced of this from such records as were available to him, for he states that "the evidence appears to me altogether satisfactory that some most fatal series of puerperal fever have been produced by an infection originating in the matter or effluvia of erysipelas."

In spite of the added knowledge as to the real cause of puerperal sepsis and the knowledge of Lister's antiseptic and aseptic technique little progress was made in curbing its incidence especially in private practice, largely because the precepts laid down by Holmes and his contemporaries were forgotten. It is a remarkable fact that at a great public dinner given by the Medical Profession to Oliver Wendell Holmes in New York in the year 1883 not one of the many speakers even mentioned his Essay on puerperal sepsis.

In 1906 Charles Cullingworth of London brought the Essay again before the Profession in a notable address in which he deplored the fact that the mortality from puerperal sepsis showed no signs of diminishing, that, indeed, it was increasing in private practice. In seeking an explanation for this he quotes from the Presidential Address of Milne Murray, delivered before the Edinburgh Obstetrical Society in 1900 as follows: "Why are the results of private practice becoming worse and worse, in spite of all that has been done for our science and art during the closing century? . . . I feel sure that an explanation of much of the increase of maternal mortality from 1847 onwards, will be found in, first, the misuse of anaesthesia, and second, in the ridiculous parody which, in many practitioners' hands, stands for the use of antiseptics. ... Before the days of anaesthesia, interference was limited and obstetric operations were at a minimum, because interference of all kinds increased the conscious suffering of the patient. . . . When anaesthesia became possible, and interference became more frequent because it involved no additional suffering, operations were undertaken when really unnecessary, on the demand of the patient or for the convenience

of the practitioner. And so complications arose and the dangers of labor increased.... Then came the antiseptic era. Here, now, was the panacea for all the dangers of childbed. All that was necessary was to dip the instruments for a few minutes in a carbolic lotion and the hands in one of half the strength for half the time, and all danger was at an end.... Normal labour is a natural process which is best left to itself, and the less the patient is disturbed with the paraphernalia of obstetrics, before or after, the better; ... until men realize this, and recognize the fact that the simplest obstetric operation demands not one whit less of care as to antiseptic precautions than is required of one before opening the abdomen, we shall get no further forward. When the practical obstetrician realizes his responsibility, and that no small share of this terrible maternal mortality of a certainty lies at his door, he has made the first step towards true progress."

When prenatal care began to be emphasized after the beginning of the present Century it was thought that, with its extended adoption, a notable fall in maternal mortality was bound to occur. There was a diminution in the number of deaths from toxemia and eclampsia but the sepsis rate remained stationary, and that from obstetrical procedures and accidents rather increased, just as it had done in the late 90's.

It is only in the past ten or fifteen years that we have got full scientific proof for the assertion that Oliver Wendell Holmes made, that puerperal fever is contagious, and justification for the precautions he enjoined for its prevention. In many of the cases and series of cases which he cites there was evidence of direct conveyance of infection from the uncleansed hands of the doctor or midwife going directly to a patient from an autopsy or from another patient already infected. But he mentions others in which such direct contamination did not occur. For instance he tells of the experience of a certain Dr. Mirriman who "was at the examination of the body of a case of puerperal fever at two o'clock in the afternoon. He took care not to touch the body. At nine o'clock the same evening he attended a woman in labor; she was so nearly delivered that he had scarcely anything to do. The next morning she had severe rigors and in forty-eight hours was a corpse. Her infant had erysipelas and died in two days." He records other instances in which days elapsed between the exposure of a doctor to infection and the occurrence of a puerperal fever in his practice. He concluded that somehow or other the doctor carried around the contagion in his person. And he was right, for we now know that certain individuals, especially those exposed to streptococcal infections of any kind, may be carriers of the organism without they themselves being affected. We know that the carrier most often harbors the organism in the nose, mouth, or throat, and that he is a menace to every parturient patient whom he attends. Dr. Frank L. Meleney of this City was one of the first to demonstrate the part the carrier plays in the dissemination of infection. In 1926 he traced a series of streptococcal infections in surgical wounds to certain individuals in the operating rooms who had an identical organism in their throats. He produced further proof when he undertook the investigation of the outbreak of streptococcal puerperal infection in the old Sloane Hospital in 1927. Since then many others have proved beyond a doubt that the nose and throat carrier is the major menace in the dissemination of streptococcal infections. In this connection it is interesting to note that in Aberdeen, the city in which Alexander Gordon described the series of infections in 1795, another series occurred in 1932-33 and that Dr. J. Smith was able to trace the cases to doctors who harbored the organism in their throats or noses. With this knowledge of the role played by the carrier we are able to safeguard our patients by taking frequent throat cultures from all obstetrical personnel and by complete masking of the throat and nose of all who attend women in labor or nurse them in the puerperium.

We now know that there are many different strains of strepto-cocci, some virulent and some non-virulent. It is the beta hemolytic streptococcus group A which is the one to be feared. When it is found in the throat or nose of an individual, he or she must cease from taking any part in obstetric practice until the organism has been got rid of. So we are just one step ahead of Holmes, who had no means of recognizing that individual until a case had actually occurred in his practice. But we still have to keep on driving these truths home for it is always difficult to get universal adoption of a technique which, when things are going smoothly, savours of frills and fussiness. We see the same things today in civilian life with our air raid precautions. They all seem so unnecessary until calamity is actually upon us.

The scientific justification for Dr. Charles White's injunction regarding cleaning of the floors and walls of rooms, the airing of bedding and fumigation with chlorine gas came only a few years ago when a namesake, Dr. Elizabeth White, working with Colebrook in Queen

Charlotte's Hospital, London, demonstrated the presence of virulent streptococci in the dust and floor and walls of rooms occupied by infected individuals, and this even after a considerable period of time had elapsed since the patient was removed. So we have re-emphasized the necessity for the segregation of all infected cases and for the establishment in every maternity hospital of an isolation unit in which such segregation can be carried out.

In his publication of 1855 Holmes in answering his critics says of his Essay that "it makes full allowance for other causes besides personal transmission. . . . It allows for the possibility of different modes of conveyances of the destructive principle. . . . It does not undertake to discuss the theoretical part of the subject." And we now have proof that there are causes of puerperal infection other than personal transmission. We know that many cases, indeed most cases of puerperal sepsis today, are not due to the aerobic hemolytic streptococcus carried to the patient from without, but to anaerobic organisms which are normal habitants of the vagina and which become pathogenic, usually in the presence of dead or devitalized tissue. This is the type of infection which frequently follows traumatizing deliveries and incomplete abortions. The prophylaxis against it is to avoid operative delivery wherever possible and, when it becomes necessary, to do it with the greatest skill and gentleness.

Some ten or twelve years ago public health authorities, and through them the lay press and the general public, became aroused at the continuing high maternal death rate in this country. Leaders in the medical profession seized upon the opportunity to do something about it. So studies were undertaken, notably one in Philadelphia and one directed by The New York Academy of Medicine. The facts brought to light by these investigations stimulated formation of similar study groups in medical societies and departments of health throughout the country. These function continuously so that every maternal death in each community is investigated and discussed by the group. In this way a large part of the profession is not only kept constantly aware of what is happening but is being instructed in the ways by which fatalities can be avoided. I believe that it is because of this, together with the splendid work being done by our own Maternity Center Association and the Maternal Health and Child Welfare Organizations that in the past five years there has been a notable and steady decline in the maternal death rate in this country. Oliver Wendell Holmes at last stands vindicated.

MY DR. OLIVER WENDELL HOLMES*

REGINALD FITZ

Boston, Mass.

there are three people in every dialogue: the real John, John's ideal John, and Peter's John. The real Oliver Wendell Holmes has been competently described by his old friend Mr. John T. Morse, although as Dr. Holmes himself said, "Think what a horrid piece of business the biographers make of a man's private history!" The ideal Oliver Wendell Holmes also has been described in a variety of ways by many admirers more gifted in the art of expression than am I. All that I can do is to speak very simply of my own Oliver Wendell Holmes—a respected teacher of the Harvard Medical School whom I appreciate more than most and for whom I have inherited an abiding affection.

Dr. Holmes, as everyone knows, came of good New England stock with distinguished medical forbears on both sides of his family tree. He had a minister for a father and was brought up so surrounded by books and bookish people that he always felt at home in a library "wherever he smelt the invigorating fragrance of Russian leather." He went through Harvard College, ranking in the upper third of his class, not a conspicuously brilliant student but, on the other hand, a better than average performer with such healthy extracurricular interests as a liking for sports and literature. He was a short person, standing only five feet four inches, according to his passport, and thus was considerably smaller than many of his friends. On this score he tended to be a little self-conscious and because of his small stature developed what nowadays would be called an inferiority complex which seemed to drive him ahead relentlessly. But he was a handsome youth, gay and witty: he smoked devoutly, sang unmusically, and drank moderately, all with a knack at writing amusing verse on the slightest provocation. These attributes combined to make him popular and able to get along with

^{*} Presented at The New York Academy of Medicine, February 19, 1943 in the Centenary Celebration of the publication by Oliver Wendell Holmes of his paper on The Contagionsness of Puerperal Fever. Thanks are due to Mr. T. F. Currier and Miss E. M. Tilton.

people. And finally, perhaps best of all, he determined to enter medicine after a year in the Law School so that he seemed to know in which direction he wished to sail.

As an undergraduate he had only played with pen and ink but it was as a law student that he became seriously interested in the art of writing. It was here that he wrote "Old Ironsides" and, as he said, first tasted the intoxicating pleasures of authorship, and was pervaded by that form of lead poisoning which invariably reaches a young author through mental contact with printers' metal.

Having made up his mind to study medicine and with Harvard in his blood, he naturally gravitated to the Harvard Medical School. He attended the medical lectures there in the fall of 1830, 1831, and 1832. In those days our process of medical education was very simple and was designed to train doctors poorly at the least possible expenditure of time, money, or effort. The course entailed attendance at two series of lectures, for four months each, in the three subjects of anatomy and surgery, chemistry, and the theory and practice of physic. On top of this was a thesis which had to be submitted and approved, and a practical examination which had to be passed. But in addition, and this was the one redeeming feature, each student before receiving his degree must have spent three years in practical work under the direction of a regular practitioner of medicine. Here, Dr. Holmes was fortunate, for he had as his preceptor, Dr. James Jackson, a man for whom he developed profound admiration. Dr. Jackson's friendship and counsel were to rank among the chief pleasures and privileges that Dr. Holmes experienced.

Instead of taking his degree in 1833, as he might have done, Dr. Holmes went abroad for nearly three years—a period in his life which had much to do with his subsequent medical development. He did not go to Germany where a future anatomist should have gone, but instead went to Paris, then the ideal training ground for the clinician. He worked under such masters as Dupuytren and Velpeau, and especially under Louis, along with a stimulating group of students from Boston, New York, Philadelphia, and various parts of Europe.

His notebooks at that time are interesting. First, while he was unfamiliar with the new language he did his best to take careful notes in English of what he heard; then, as he became more proficient, he grew more confident, until finally he was able to say that French had

become a second mother tongue to him and that he even could think in it. Hence his lecture notes towards the end of his stay abroad were all written in that foreign language.

It is obvious that he worked hard in the clinic or pathological laboratory and throve on having the whole vista of modern scientific medicine opened before him by wise instructors. In 1834 he wrote home:

"Nearly five hours in the day I pass at the bedside of patients, and you may imagine that this is no trifling occupation, when I tell you that it is always with my note-book in my hand; that I often devote nearly two hours to investigating a difficult case, in order that no element can escape me, and that I have always a hundred patients under my eye. Add to this the details and laborious examination of all the organs of the body in such cases as are fatal—the demands of a Society of which I am a member—which in the course of two months has called on me for memoirs to the extent of thirty thick-set pages—all in French, and almost all facts hewn out one by one from the quarry—and my out-of-door occupations have borne their testimony."

The Society of which he spoke reminds one of our present American Society of Clinical Investigation. It was formed in 1832 by a group of youngsters eager to advance medical knowledge and to report their own work. It was called the Société d'Observation Médicale. Louis was the honorary President and James Jackson, Jr. was one of the founders. At the various meetings which were held frequently, different members presented original papers and these were discussed freely.

Perhaps the chief advantage of this medical fraternity was that each member came in direct contact with Louis. They learned from him what Osler called the numerical method of clinical investigation: to study meticulously a series of similar cases, going into all the particulars of the condition under scrutiny, its cause, its various symptoms, its pathology, and the effect of treatment. "The edifice of Medicine," Louis kept repeating, "reposes entirely on facts. The truth cannot be elicited except from facts which have been well and carefully observed."

To end up with, Dr. Holmes made the grand tour and no doubt compared, not too favorably, what he saw of the capitals of Europe with Beacon Hill and the Frog Pond. But he returned home as well trained and competent a young doctor as you could ask for, bursting with ambition, filled with high ideals, and prepared to demonstrate to his friends that he was wedded to the profession of medicine.

Thus my Dr. Holmes arrived in Boston at the end of 1835, twenty-six years old, a dynamo of energy with his small body, his inferiority complex, his hypersensitiveness to lead poisoning, his foreign training, and his fixed ambition to be second to none in the profession of medicine

there. Now he was ready to go to work.

Dr. Holmes was easily a hundred years ahead of his time. Thus in thinking of him one should regard him as a graduate of Harvard in the Class of 1929 and facing his particular problems much as did any of our abler young Bostonians of that period who graduated from the Harvard Medical School, who had, let us say, an internship in the Massachusetts General Hospital and three years or so in the Rockefeller Hospital, the Mayo Clinic, or some equally alive place outside of Boston, and who then wished to begin their careers.

The first thing that Dr. Holmes had to do was to get his degree. He arrived in Cambridge about Christmas time and knew that the Statutes of the Medical School demanded that any candidate "shall four weeks previous to the day on which he presents himself for examination, have given written notice of his intention to the Dean of the Faculty, and at the same time shall have delivered or transmitted to the Dean a dissertation, written by himself, on some subject connected with medicine." If the dissertation was approved, the candidate then had to suffer a general oral examination. If he leaped this hurdle his name was passed upon by the Senatus Academicus and finally he was admitted to the degree "at a public Commencement holden on the Wednesday next succeeding the day of the examination, on which occasion an address shall be delivered by some one selected for this purpose by the Medical Faculty."

In '36 the examination was to be held on the first Wednesday in February so that Dr. Holmes had to submit his thesis in early January, and this he did, writing a paper on Pericarditis in the space of three or four days. Our Faculty book says that on February 4th Mr. Holmes was approved for public examination. On February 11th he received his degree.

The next thing to be done as an enterprising young doctor was to join the proper medical clubs: the Massachusetts Medical Society, the Boston Medical Society, and the Boston Society for Medical Improvement. Dr. Holmes wasted no time. By May he was attending meetings of these organizations, listening to deliberations, and fraternizing with older physicians.

Clearly, he had to burn up some of his restless energy. He was not associated with any Medical School or Hospital and building up practice in Boston is notoriously slow, so that he had plenty of time on his hands. He happened to see in one of the back numbers of the Boston Medical

and Surgical Journal an announcement of the Boylston Prize Dissertation—an annual affair at the winning of which his brother-in-law Dr.

Usher Parsons held the world's record, having won four prizes in a row.

On or before April 1st, competitors were directed to submit for the prize of that year a paper on "How far are the external means of exploring the conditions of the internal organs to be considered useful and important in medical practice?" or "To what extent is an active medi-

cal practice useful in the common continued fevers of the country?"

And on or before the first of April '37, competitors a year hence might be awarded the prize by most wisely answering "What is the Nature of Neuralgia and what is the best mode of treating it?" or "To what extent, and in what places has intermittent Fever been indigenous in New England?"

Dr. Holmes got right to work on the first question. His paper on exploration of the internal organs was duly written in time for Dr. J. C. Warren to receive it before the stipulated date.

Dr. Holmes was nobody's fool. He knew that to get ahead in Boston

one must somehow catch the public eye or be doomed to mediocrity.

In '36, we of the Massachusetts Medical Society had a little trouble. Dr. John S. Bartlett, one of our members, it was reported, "gave countenance to an itinerant charlatan whose character and pretensions have been fairly shown to deserve the contempt of all honorable men." Accordingly, the Society determined to expel him on the ground of unethical conduct. The Boston Medical Society, of which he also was a member, decided to follow suit but, unfortunately, after having expelled the poor man, made the mistake of allowing him to have the privilege of the floor. Dr. Bartlett made a speech: he said that perhaps he had been indiscreet but at least that he could mention by name-and he proceeded to do so-several members of the Boston Medical Society who were as bad as he, if not worse, who were in the habit of consulting with doctors who were not members of the Massachusetts Medical Society, and he even went on to say that some of them were known to have advertised quack remedies in the public press. If he was to be kicked out, why not they as well?

Things at this juncture were a little tense. Dr. Holmes, the youngest member present, now rose to his feet and remarked that according to parliamentary procedure further discussion was a waste of time since Dr. Bartlett was no longer a member of the Society. The older men

thought this a reasonable way of heading off Dr. Bartlett and at once looked with approval on young Holmes as perhaps having the makings of an adroit medical politician.

Dr. Bartlett, however, felt that he had been treated unfairly. He proposed to sue the Massachusetts Medical Society for reasons not unlike the recent unpleasantness in which the American Medical Association has been engaged. Dr. Holmes had no wish to become involved in a lawsuit though he was not averse to seeing his name in print as a physician of standing in the community. Thus his first publication on any medical matter appeared in the Boston Medical and Surgical Journal for Wednesday, June 22, 1836. Here it is quoted in full. It contains one sentence a hundred words long:

"To the Editor of the Boston Medical and Surgical Journal. Sir—As the remarks attributed to me in the report of proceedings of the Boston Medical Association have been considered by Dr. J. S. Bartlett as a personal attack, it may be well to say that my observations were intended by myself, and understood by the reporter, to apply to Dr. Bartlett only in his capacity of member of the Association, for the common privileges and intercourse of which he had been declared unfit by expulsion, and in which his character as a member having been forfeited, he could no longer be restrained by a proper responsibility in preferring his numerous accusations.

Respectfully yours

O. W. Holmes"

Boston, June 15, 1836.

In the summer of '36, Harvard was to celebrate its bicentennial. There was to be the ordinary Commencement and then, a week later, a day of celebration by the alumni, starting with a service in the church in the morning and exercises in the afternoon (with food and drink) which were to be held in a big tent in the Yard. The proposed program included so many speeches as to necessitate the employment of three presiding officers.

The Powers That Be knew that Dr. Holmes had been away for some time and recalled that in College he had written verse worth reading. Hence the Phi Beta Kappa invited him to read the poem for their annual meeting. And the Alumni Association asked him to write something lighter for the bicentennial celebration to leaven the ponderousness of the speakers that undoubtedly would be inflicted upon the long-suffering audience and the three toastmasters in the tent.

Dr. Holmes must have labored hard on the Phi Beta Kappa poem because Harvard's most competent critic, the Reverend John Pierce of the Class of 1797 who attended forty-six consecutive Commencements and made a record of each of them, wrote of this one: "After a suitable interlude by the band, Oliver Wendell Holmes, M.D., of the Class of 1829, delivered a beautiful poem of one hour and ten minutes, committed to memory, and uttered with charming ease and propriety." To become letter perfect in a poem of that length was in itself no mean performance.

And as for the alumni exercises a week later: they lasted from two in the afternoon until eight in the evening. Anyone who has read the proceedings, who can imagine himself drinking this or that all day, and who can hum "The Poacher's Song," will appreciate how well, in the midst of a lot of rather dull speakers, Dr. Holmes must have sounded as he sang to that tune, even unmusically, with everyone joining in the chorus,

"And who was on the Catalogue
When College was begun?
Two nephews of the President
And the Professor's son;
They burned a little Indian boy
As brown as any bun;
Lord how the seniors knocked about
The freshman class of one!"

To cap off all this and to convince any doubters in the medical profession that Dr. Holmes was no ordinary young man, the Boylston prize winners were announced at about that time. The Boston Medical and Surgical Journal for August 24th described how Dr. Holmes had been awarded the prize but that there were two other dissertations on the same subject of so high a character that this year three prizes had been awarded by an unanimous vote, one to each of these three authors. Dr. Holmes' colleagues were Dr. Robert W. Haxall of Richmond, Virginia, and Dr. Luther V. Bell of Derry, N. H.

Dr. John Warren had remarked of vaccination shortly after its introduction by Dr. Waterhouse, that it was making a good deal of noise around Boston. One might say the same of Dr. Holmes after he had been there a year. To be sure, his practice was inconsiderable but he had done so many more spectacular things than had any of his contemporaries that people in high circles already were talking about him. And the year '37 proved auspicious by his appointment to the staff of

the Boston Dispensary and by his winning a double-header in the Boylston prize line. When this was announced, the Boston Medical and Surgical Journal admitted, "It is almost useless to contend with him in an enterprise of this kind." From which one may assume that his method of writing already had made a permanent dent in the minds of the medical profession of New England.

Dr. Holmes found time to remain on the staff of the Dispensary for only a year for he had other irons in the fire. He wished to become a teacher. As far as one could see, the professorial chairs of the Harvard Medical School were filled until Divine Providence intervened. Thus Dr. Holmes felt obliged to look for opportunity elsewhere.

At the end of the spring term of '38 the Dartmouth Medical School found itself in trouble. Changes had come about as a result of which the Trustees were compelled to find a new Professor of Anatomy. I suspect that Dr. Usher Parsons, a former member of the Faculty, who knew Dr. Holmes' aspirations, may have been consulted and that perhaps he suggested the name of his brother-in-law, an untried young man without pretense to great anatomical knowledge, to be sure, but from his record so far, obviously a man of considerable promise. In any event, Dr. Holmes was offered the post and accepted it. On August 7th he wrote to Dr. Parsons: "I have just had official notice of my appointment as Professor of Anatomy in Dartmouth College. Of course I am not obliged to reside there except during lectures. I think this is a very agreeable appointment, and as I do not lecture until next August, I shall have plenty of time to get ready."

In Boston, too, there also seemed a chance for an imaginative person to do something new.

The teaching at the Harvard Medical School was irritatingly poor to a man thinking a hundred years ahead of his times. Several "private" medical schools in Boston were doing good business. Why not have another and make it better than any medical school so far established?

It was said of Dr. Jacob Bigelow, the Professor of Materia Medica at Harvard, that he was one of the most charming, intelligent, and versatile people in Boston. He and Dr. Holmes knew each other well. In the fall of '38, they decided to open what was to be called the Tremont Medical School. From the outset this was to be sort of a progressive branch of the Harvard Medical School. Dr. Holmes was to teach Pathology and Physiology; Dr. Bigelow who, as has been mentioned,

held a professorship at Harvard, was to teach the same subject, Materia Medica, and also Practice of Medicine; Dr. Edward Reynolds, who had substituted for Dr. John C. Warren at Harvard while he took a year's holiday, was to carry on in Anatomy and Surgery; and Dr. David Humphreys Storer, later to succeed Dr. Channing as Professor of Obstetrics at Harvard, was to be responsible for Midwifery and Chemistry. Dr. Holmes and Dr. Storer represented the young and aggressive wing of this small faculty, counterbalanced by Dr. Bigelow and Dr. Reynolds as the conservative element. As they planned the enterprise they arranged the curriculum cleverly. It was to dovetail with Harvard as much as possible, operating at a time of year when lectures were not being held at Harvard and supplementing what Harvard appeared to lack. One course, for instance, was to start in March when nothing else was going on and, as Dr. Holmes said later, in the windy month-which was selected on account of the great number of puffs it was expected to give the School for nothing. Dr. Holmes and his new faculty resurrected an old plan under which the Harvard Medical School had started but had forgotten. They proposed in their School that Medical Education should be arranged as an orderly discipline instead of as a haphazard conglomeration of lectures; in the first year, anatomy, chemistry, physiology, and pathology should be taught to beginners, followed by clinical work in the second year and by a voluntary third year, the student by this time being assumed to realize his deficiencies and able to decide for himself in what subjects he needed help.

This venture proved successful from the very start and, in fact, played an important part later in reforming the Harvard Medical School. It is interesting that during the years in which the School existed, Dr. Holmes taught rather more of clinical medicine and pathology than he did of anatomy though he did offer instruction in microscopical anatomy.

By '38, too, Dr. Holmes was beginning to make himself felt as a doctor: not the ordinary kind of practitioner by whom small fevers were gratefully received but as a modern internist who was prepared to see only a few cases, to follow to the autopsy table those that were fatal, who wished to study disease rather than to treat it, and to advance medical knowledge, as Louis had said, by eliciting truth through the establishment of facts which were well and carefully observed.

The following report taken from one of his Case Books serves well

to illustrate the type of clinical work in which Dr. Holmes believed.

Disease of Heart-Exam. with Dr. Inches.

June 30th S. B. Act. 12-Elliot Street

Saw on entering room a slender girl with reddish hair and light complexion, very pale, a good deal emaciated, sitting up in bed. Countenance pretty easy, breathing not very labored—no lividity. Ascites with great oedema of legs. Right jugular veins (external) considerably swelled—arterial and venous pulsations of this side very apparent—on left side nothing unusual in the same region.

Inspection of chest. Left nipple ½ inch or more higher than right. Cardiac region somewhat prominent but not distinctly defined; intercostal spaces not prominent or even filled up—great motion of parietes during heart's action.

Percussion. Much flatness in cardiac region extending a good ways externally—towards side—

Auscultation. Pulsations of heart rapid (120); second sound dull, without any of its sharp character. Bruit de soufflet, seeming to attend first sounds; this is not harsh, and is most distinctly heard in the left back—much more so than in front. Sound heard also in right back. Impulse in praecordial region very heaving and forcible. Rhythm and force of heart's pulsations perfectly regular. Pulse very small and wiry—120. Resp. about 36. No remarkable derangement of digestion or nervous functions. Urine very small in quantity and high coloured, turbid. Has not had any fainting fits since Dr. Inches attended her, but one, not very clearly described some weeks since.

A fine crepitous or subcrepitous rattle exists towards the post, and inf. edge of left lung—where a little dulness on percussion was suspected.

This patient had three months ago pneumonia of left side and pericarditis; this was attended by Dr. Bethune. Three weeks since her present difficulties began with oedema of the lower extremities. Some pain had been referred to edge of cartilages of left rib. No depression exists there or at epigast, to denote an adhesion of heart and pericardium—

She has been using digitalis and within a few days the dyspnoea has diminished, and she slept with her head in a more level position.

Recommended Hyd. Labmur, and Squills—Dr. Inches tells me that about the 11th of July there came on cough with bloody expect, but not rustly like that of pneumonia—though viscid.

Yesterday (July 20th) the pulse, which had remained at 120, rose to 144, and the hands were found swelled, day before yesterday for the first time. The oedema has encreased, the strength diminished.

To-day (July 21st) went to see this patient with Dr. Inches. Found her aspect much as before; very thin and pale; abdomen much distended by fluid, right jugular full as before; sitting up, cannot lie down, resp. rapid, p. 116-130 or more, pretty full and sharp as from irritations; coughs frequently; expect. much fluid blood with mucus, which is semitransp. and does not resemble the sputas of pneumonia. The expression of the countenance is not distress, the voice is pretty good and the patient very gentle and obedient.

The puls. of heart appears to me less strong and the sounds less marked than at the previous examination; the bruit de soufflet still exists.

At the lower and posterior part of the right lung is some obscurity on percussion, more than on the other side, which however does not seem to resound quite as much as natural.

At this part of the right is a fine crepitous rattle after cough, but there is no bronchial resp. at the same parts, and no broncophony. Some mucous rattle seems to be heard in the left back, and the sonorous and sibilant rattles are heard, very generally on both sides.

The sound on percussion is good at the right summit (on clavicle and below) but the voice sounds much more both in the subclav. and accom. regions of this side than on the other side at the same points. Still, the resp. is vesicular.

Sept. 4th. Died this morning after much suffering toward the close of life.

Autopsy. Externally, great emaciation—abd. much distended—veins of thorax and neck quite full, skin of abd. and lower extremities streaked by serous distension which seems to have separated its fibres—two very deep sloughs over ischiatic protuberances. Abdomen contains perhaps a gallon of yellow transparent serum—no false membranes. Liver presents nothing remarkable—neither do the kidneys. Heart quite large—all the cavities seem dilated. L. ventricle about 6 French lines in thickness right 2 lines. Valves of aorta and pulmonary artery healthy. The tricuspid valve seems natural—closes the orifice pretty exactly when water is poured in. The mitral valve (one of its folds is opake containing several indurations (Note)—In both these valves one of the folds was much ampler and freer than the other. Pericardium contained about one ounce of yellowish serum—no false membranes or trace of pericarditis.

Left lung free; lower lobe condensed, not hepatised nor splenizated—containing much serum, aerated—no tubercles. Right lung presented extensive cellular adhesions—upper lobe healthy, lower lobe universally solidified with tubercular infiltration, distinct small tubercles—one or two large masses and one small cavity as big as a shelled almond perhaps. A few ounces of serum in left pleura.

Head not examined.

Dr. Holmes lectured at Dartmouth for two terms: he was becoming too busy at home to stay longer and he wanted larger pastures. The Dartmouth experience gave him a chance to get the hang of the lecture-room—he badly needed practice here, according to his colleague Dr. Elisha Bartlett—and training in being the administrative head of a university department. But it was too small a place.

In '39 the University of Maryland offered him the chair of surgery and he considered the possibility of being a surgeon in Baltimore while he was an anatomist in Hanover, which, when all was said and done, was a novel thought for a young doctor who was neither surgeon nor anatomist. Finally, he rejected the idea since he knew that at heart he was a Bostonian and that what he really longed for was a post at Harvard.

Here things looked gloomy for an impatient person wishing to climb the academic ladder quickly. All Dr. Holmes had to do was to apply the numerical method of Louis to the Harvard Medical School in order to realize how slim were his chances.

Dr. Jackson was well-nigh certain to be succeeded by Dr. Ware in medicine, and Dr. Warren seemed hale and hearty for several years to come, with Dr. Hayward a likely successor in anatomy and surgery. Thus the only course for Dr. Holmes to follow was to devote his energies to the Tremont Medical School and to the practice of medicine, leaving the future to Fate.

| Name | Subject | Born | Appointed Professor | Age in 1840 |
|-----------------|---------------------------------------|------|------------------------|----------------|
| James Jackson | Theory and Practice | 1777 | 1812 | 63 |
| J. C. Warren | Anatomy and Surgery | 1778 | 1815 | 62 |
| Walter Channing | Midwifery Medical Jurisprudence | 1786 | 1815 | 54 |
| Jacob Bigelow | Materia Medica | 1787 | 1815 | 53 |
| George Hayward | · Clinical Surgery | 1791 | 1835 | . 49 |
| John W. Webster | Chemistry | 1793 | 1826 | 47 |
| John Ware | Adjunct in Theory and Practice | 1795 | 1836 | 45 |

THE HARVARD MEDICAL FACULTY IN 1840

To a man who was a dynamo of energy, with hypersensitiveness to lead poisoning and a fixed ambition to be second to none in the profession of medicine in Boston, opportunities were bound to occur. The first came in '39 in the early days of the Tremont Medical School. Messrs. Little and Brown approached Dr. Holmes and Dr. Bigelow. A new medical text seemed needed in Boston, they had just obtained the publishing rights for an American edition of Hall's Principles of the Theory and Practice of Medicine and would not Drs. Holmes and Bigelow undertake the editing and re-writing of this book?

Half a century later William Osler was placed in a very similar position by the Appleton Company, and finally, as he expressed it, sold his brains to the devil and signed the contract. Drs. Holmes and Bigelow did the same thing. The textbook was printed in the fall. It received a flattering review from the Boston Medical and Surgical Journal though I regret to say never became a very popular volume. But to produce it meant work.

In '42 Dr. Holmes became interested in Homeopathy and tilted at this windmill with all his might. In '43 he read his paper on the Contagiousness of Puerperal Fever before the Boston Society for Medical Improvement. People remembered "The Poacher's Song" and expected him to produce verse or sing amusing songs at all possible gatherings.

Moreover, by now his practice was almost too large and he was in great demand in Boston society, many people feeling about him as did Dr. Bartlett: "His mind is quick as lightning and sharp as a razor. His conversational powers are absolutely wonderful. His talk at table is all spontaneous, unpremeditated, and he pours himself forth—words and thoughts—in a perfect torrent. His wit and humour are quite lost in the prodigal exuberance of his thoughts and language." Finally his reputation as an interesting speaker in other fields than medicine grew and he began to tour the country as guest of the evening at "Lyceums." One suspects that he may have done this for FAME, which in the vernacular of the day did not mean fame in the ordinary sense of the word but Fifty And My Expenses. Thus with practice, teaching and talking, he grew busier and busier.

'46 was an important year. President Everett became head of Harvard University. The Massachusetts General Hospital was to add new wings to the old Bulfinch Building and, in the prospect of an increase in the number of patients, enlarged its staff, appointing Dr. Holmes as one of its physicians. Ether was used for the first time. Dr. Holmes was so overwhelmed with work that he could allow himself but a single week's vacation, which meant that such a pace was too fast to keep up indefinitely.

These events, apparently unrelated, somehow contrived to have much to do with Dr. Holmes' future. Dr. Warren resigned from the Medical School in February '47, perhaps because he believed that to have introduced ether marked a good end-point to a useful career in surgery or because he thought the new President of Harvard and the enlarged Hospital should be given free hands. Dr. Holmes was invited to become Professor of Anatomy and Physiology and accepted with joy, in part, perhaps, because he hoped that in so doing he would be able to concentrate his various interests and accomplish more than was otherwise possible. Thus he settled into a professorial armchair in Harvard towards which he had been aiming for eleven years.

There is little to be said of his subsequent career beyond what is familiar to everyone. His reputation as an author soon became worldwide, and outshadowed everything else.

While he was at Dartmouth he had worked out a formula for the teaching of anatomy and physiology to which he adhered until he retired. Anatomy should teach the structures of living bodies, the tissues

of which they are composed, the organs formed by these tissues and their mechanical relation to each other; physiology should inquire into the mode in which these living tissues and organs perform their various offices. The chief duty of a professor was to guide his students into the pathways by which they could learn more. They must respect knowledge for its own sake and not for any immediate practical purpose to be gained by its acquisition.

He believed that most effort should be directed to the lower half of each class where obviously the best teaching was most badly needed. Thus he tried to make his lectures clear and understandable, simple, and as lively as possible so that he could animate dry bones or give color and vitality to dead tissues. He was interested in what he termed transcendental anatomy and through it he preached to class after class the value of high ideals, integrity of character and fearlessness in meeting the unknown. He acquired the reputation of being our most fascinating lecturer. Stories of him are legendary in the Harvard Medical School and are handed on from one generation of students to the next.

When he accepted his appointment at Harvard he said, "I will do what I can to prove myself not unworthy of the good opinion implied by this choice. None of us can accept any office in our ancient University without a feeling of pleasure and pride." He lived up to this. He was a devoted servant as Professor, Dean of the Medical School, Professor Emeritus, and Overseer.

As he drifted from being a well-trained young internist to being a professor of anatomy and physiology and thence to being a distinguished author, his influence on American medicine became increasingly strong. Not only was he able to think far ahead of his time but also he could express his thoughts so that they could be read and understood. There was scarcely an important development at Harvard or in Boston medicine during his lifetime in which he did not play a part; and whenever an address had to be written, a useful undertaking begun, an appeal made, a poem read, an obituary notice phrased neatly, his pen was ready to serve. For Dr. Holmes had Harvard spirit. He did all that he could to carry on the purpose for which the university was founded, "to advance learning and perpetuate it to posterity."

One hundred years ago Dr. Holmes published his paper on the Contagiousness of Puerperal Fever in celebration of which we are meeting this evening. Sixty years ago he attended a dinner in New York at



Delmonico's, given in his honor by some two hundred New York doctors many of whom were members of the Academy. They pretended to accuse him of having accepted the invitation in verse and of illustrating it with an original drawing though his "telegram" of acceptance was not written in his own handwriting, was dated April 1st and the drawing was unsigned.

The President, Dr. Fordyce Barker, was in the chair. There were speeches, compliments, general jollification, and, of course, a poem by Dr. Holmes.

Dr. Andrew Smith, later to be elected President, expressed very nicely how my Dr. Holmes would wish the members and friends of The New York Academy of Medicine always to remember him:

"You've heard of the Deacon's one-horse shay Which, finished in Boston the self-same day That the city of Lisbon went to pot, Did a century's service and then was not.

May the fate of the chaise be the fate of our friend.

May he never break down and never wear out,

But a century old or thereabouts,

Not feeling the weight of the years as they fly, Simply stop living when ready to die."

OBSTETRICS YESTERDAY AND TOMORROW*

ALAN F. GUTTMACHER

man read a paper, entitled "The Contagiousness of Puerperal Fever," before the Boston Society for Medical Improvement. Of course, the young man was Dr. Oliver Wendell Holmes, whose medical importance has been somewhat obscured by his far greater literary eminence. Young Holmes was a New England product-born in Cambridge, graduated from Harvard, and grounded in Boston medicine. His rather primitive American medical training was improved by two years residence abroad; here he absorbed the best medicine of his day by studying under the great Dr. Louis in Paris and visiting the medical centers in England, the Low Countries and Italy. On his return to Boston in 1835 he sought practice, but few patients sought him. Socially charming, brilliant in conversation, the writer of gay little poems, he seemed to the grave Bostonians not sufficiently serious. Even during these early years in Medicine he leaned more heavily upon the pen, than upon the lancet, for previous to 1843, he had already written papers attacking homeopathy, an essay on neuralgia, a plea for his colleagues to use auscultation and percussion more extensively, as well as a valuable treatise on the malarial fevers of his native New England.

Holmes' essay on "The Contagiousness of Puerperal Fever" was all the more remarkable since it was constructed almost wholly on arm chair logic; his opportunities for practical experience in the art of midwifery were very deficient. He was a thorough student and knew intimately the medical writings of contemporaries and recent predecessors. These he digested, reconstructed and amended into a logical essay on how puerperal fever was acquired and what to do to prevent it.

Since the time of Hippocrates, medical men had been earnestly con-

^{*} Itom the Departments of Obstetrics of the Johns Hopkins Hospital and Medical School and the Sirai Hospital, Baltimore. Read February 19, 1943 in the Centenary Celebration of the publication by Oliver Wendell Holmes of his paper on The Contagiousness of Puerperal Fever.

cerned with this dreadful malady. Hippocrates' fourth case in the first book on Epidemics, written four centures before Christ, details the tragic clinical course of Thasus, the wife of Philinas, who died in coma twenty days after the birth of a beautiful daughter. It takes little imagination to reconstruct the anguish of this young husband, over twenty-three hundred years ago, as well as the sad helplessness of Hippocrates, her physician. An untimely death is always tragic, but death in the process of giving life, is ironic and superlative tragedy. Observing a healthy, vigorous young woman begin to wither forty-eight hours after her apparent safe deliverance, and then to watch her slip into the grave, is an unforgettable experience to all descendants of Aesculapius. And Holmes was no exception.

The glimmerings of the real source of puerperal infection were foreshadowed in the writings of White of Manchester and Gordon of Aberdeen. The works of both were known to Holmes and quoted by him. In 1773 Charles White ascribed puerperal fever to two causes: a putrid atmosphere and too long confinement of the patient in the horizontal position. His advice to prevent this pestilence was as follows:

"As soon after the woman is delivered as it can be conveniently done, clean linen should be put about her, she should be left to the utmost perfect quiet of body and mind . . . no visitors . . . should be allowed to enter the patient's chamber. A number of people, besides preventing repose, foul the air . . . The chamber door, and even the windows . . . should be opened every day . . . The room should be brushed, and the carpets taken out every day to be cleaned and aired . . . The patient should lie very high with her head and shoulders, and should sit up in bed many times in a day . . . The sooner she gets out of bed after her delivery the better; even on the same day if possible."

Alexander Gordon published his important treatise two decades later, in 1795. To him is given credit for first clearly demonstrating the infectious nature of puerperal fever.

"But that the cause of the epidemic puerperal fever... was not owing to a noxious constitution of the atmosphere, I had sufficient evidence; for if it had been owing to that cause, it would have seized women in a more promiscuous and indiscriminate manner. But this disease seized such women only as were visited, or delivered, by a practitioner, or taken care of by a nurse, who had previously attended patients affected with the disease.

"In short, I had evident proofs of its infectious nature, and . . . as readily communicated as . . . the small pox, or measles.

"It is a disagreeable declaration for me to mention, that I, myself, was the means of carrying the infection to a great number of women." So much for Gordon's ideas of the cause. His theories of prevention were as simple and direct:

"The patient's apparel and bed-clothes ought, either to be burnt, or thoroughly purified, and the nurses and physicians who have attended the patients affected with the Puerperal Fever ought carefully to wash themselves, and to get their apparel properly fumigated before it be put on again."

It is to be remembered that this was still the eighteenth century. Gordon's findings, theories and recommendations should have gained widespread acceptance. But they did not.

On this side of the Atlantic leading opinion was averse to the contagious nature of puerperal infection. Let us visit the Philadelphia of one hundred years ago. Hugh Lenox Hodge at forty-seven had been the Professor of Midwifery in the University of Pennsylvania for eight years, and fifty-one year old Charles Delucena Meigs, the Professor at Jefferson, for two. At this time Philadelphia was the obstetrical womb of America and the opinions which issued forth from her became American obstetrical dogma. Hodge and Meigs disagreed about many things, but they were united in their conviction of the noncontagious nature of childbed fever. They taught it, practiced it, and wrote it.

In such an American medical setting young Holmes fearlessly, logically declared his equally unshakable conviction that childbed fever was contagious. His essay is the more remarkable when we recall that more than a quarter of a century had to pass before microbes or bacteria were first destined to be seen.

My assignment on your program prevents extensive quotations from his paper, however, allow me to quote a few of its most forceful sentences. The argument having been set forth and proven in the earlier portion of the essay, Dr. Holmes concludes with specific rules to prevent the spread of this disease.

"On the occurrence of a single case of puerperal fever in his practice, the physician is bound to consider the next female he attends in labor, unless some weeks at least have elapsed, as in danger of being

infected by him, and it is his duty to take every precaution to diminish her risk of disease and death.

"If within a short period two cases of puerperal fever happen close to each other, in the practice of the same physician, the disease not existing or prevailing in the neighborhood, he would do wisely to relinquish his obstetrical practice for at least one month, and endeavor to free himself by every available means from any noxious influence he may carry about with him.

"Whatever indulgence may be granted to those who have heretofore been the ignorant causes of so much misery, the time has come when the existence of a private pestilence in the sphere of a single physician should be looked upon, not as a misfortune, but a crime; and in the knowledge of such occurrence the duties of the practitioner to his profession should give way to his paramount obligations to society."

Holmes made no claim of originality for his views and fifty years later in a letter read at the dinner of the American Gynecological Society, he wrote: "I do know that others had cried out with all their might against the terrible evil, before I did, and I gave them full credit for it. But I think I shrieked my warning louder and longer than any of them." What he should have written is: "I shrieked my views more logically."

Holmes' views did not pass unnoticed by America's two leading professors of obstetrics. Meigs referred to them as "the jejune and fizzenless vaporings of sophomore writers." He said he would rather attribute deaths from childbed fever "to an accident, or Providence, of which I can form a conception, rather than to a contagion of which I cannot form any clear idea." Hodge begged his students to divest their minds of the dread that they could ever carry the horrible virus.

Holmes lived half of the hundred years which have transpired since his essay was first published. If he had been granted the immortality of the Gods, no doubt he would be in a perpetual state of surprise to see how radically the art of midwifery has progressed in the hundred years since 1843. Let us review some of these advances, and then formulate some of the problems which will concern the century to come.

We are in the fortunate position of being able to state exactly the up-to-the-minute obstetrical practice in 1843, for the year before. Dr. Meigs had published the second improved and enlarged edition of his three year old text book. It bore the bombastic title of "The Philadel-

phia Practice of Midwifery." It includes all that Philadelphia, that is America, knew of obstetrics at this time.

To those well trained in our art it comes as a shock to realize that not a single line of this 408 page treatise is concerned with prenatal care. The only prenatal care a pregnant woman got in 1843 was self applied. Each literate family had at least two books, the Bible and one of the many family Medical Advisers, successors to such Seventeenthcentury favorites, as Queen Elizabeth's Closet of Physical Secrets. These books advised about diet during pregnancy, clothing, the bowels, etc., with the same brevity as the diagnosis of measles or the treatment of croup. The woman only saw her doctor if she had fits or began to bleed. If no such complication arose the first knowledge the doctor had of his patient was a knock upon his oaken door by a wide-eyed lackey or a distraught husband. Then the race began between the doctor's big bay horse and the stork.

It is amusing, but hardly cricket, to write a book review one hundred years after the publication of a scientific text, but if we use the present state of our obstetrical knowledge as the yardstick, we would have to charge Dr. Meigs' text with many serious omissions. There is no reference to the measurement of the pelvis in the living subject, although the normal measurements of the dried pelvis were known. X-ray measurement of the pelvis was not to be used for eighty years. In 1843 obstetricians did not test the urine; no attention was paid to the weight gain, and, of course, blood pressure was only thought of as Stephen Hales' experiment with a column of blood pushed skyward in a glass tube which had been inserted in a horse's artery.

Pain relief during labor, twilight sleep and its extensive progeny of variations was not administered until 1905, though for a long time the occasional patient had self administered it by indulging excessively in spirituous liquors. Anesthesia in obstetrics had to wait for Dr. Simpson's chloroform and the year 1847. Surgical asepsis did not exist until the middle of the eighties, and it came to obstetrics late among the surgical branches. The sterile-gowned, rubber-gloved, white-masked obstetrician would have looked to Holmes and Meigs like a ghost at a masquerade. Ergot to arrest bleeding after delivery was just coming into use in 1843, but the discovery of the complemental drug, pituitrin, had to wait sixty-five years.

The treatment of surgical and obstetrical shock by fluid introduced

into the veins had to wait a full fifty years, and transfusion of blood at least twenty more. At this time delivery by Cesarean section was a procedure of last resort, and practically synonymous with a death certificate; for in 1843 it was fatal in more than three out of four cases, in contrast to 1943 when successful in more than 95 per cent. Obviously the sulfonamide drugs had not been dreamt of, nor the RH factor in erythroblastosis. One could elaborate on the progress of obstetrics from 1843 to 1943, but without my doing so you must grant that Holmes initiated a magnificent Century of development. There is no question that 1943 is a much safer and pleasanter year to have a baby than was 1843.

Despite this there remains an imposing list of obstetrical riddles for which the coming Century might furnish the answer. Many of the most fundamental problems of my art are as indifferently understood today as they were one hundred years ago. We do not know what actually causes the onset of labor, and until we do the prevention of premature labor and the effectual treatment of poor, inert labor pains must wait. The toxemias of pregnancy, the group of pregnancy complications associated with high blood pressure, present a major unsolved medical problem. Infections with bacteria which are resistant to the prowess of the sulfonamide drugs still cause hundreds of deaths. These and kindred problems are of particular interest to a purely medical audience, and so for the few minutes remaining I shall discuss matters which have equal interest to layman and physician.

It is my hope that the Century to come will go far in solving the medical-social problems associated with childbearing and the strengthening of the family. Let us first phrase our primary medical-social objective in this field, and then discover what factors can be brought to play which will cause its realization.

Our aim is the safe birth of physically and mentally normal children, in a number consistent with the wishes and intellectual and social capacities of the parents. These children to be so spaced that they will have the best likelihood for maximum development, and their mothers the apportunity for complete physical and emotional convalescence bet seen births. No one, even the most conservative among you, can say this is a radical aim.

What actors retard its realization? One is the partial domination of the church over matters medical. After a long and persistent struggle

we have severed the state from the domination of the church, but the church can still stay our hands in essential problems of health. If we view this unemotionally, it has a certain comic element. Well-meaning, highly moral gentlemen of the cloth, with no medical background, can dictate to equally well-meaning and equally moral physicians, that all women, irrespective of religious affiliations and beliefs, must breed to their maximum reproductive efficiency. The result is that government health agencies, which really should supervise a comprehensive program, including contraception, sterilization and pregnancy spacing, shy away from this responsibility as though it were a time bomb.

The second influence to retard the realization of our aim, is the laissez faire attitude of the medical profession. Doctors are a peculiar combination of the selfless and the selfish, of the radical and the conservative. A doctor will give unbegrudgingly and unstintingly of his time and effort to heal some poor, louse-infested beggar, but he is afraid to take a forceful stand, which he knows is right, on some controversial issue. He is afraid it may injure his practice or his standing among his colleagues. A doctor is radical when it comes to science; he is the first to modify an accepted treatment in the light of the newest discoveries, yet when it comes to social problems he is at least twenty years behind the front line.

A third inhibiting influence is an ignorance of fundamental facts. We know the intricacies of treating diabetes with insulin and crysipelas with sulfadiazine, but we don't know so simple and important a thing as the safest interval between babies, i.e., safest for both the mothers and the babies. In the field of reproduction there are lots of "don't knows." We don't know a completely reliable contraceptive agent or technique to put into the hands of the unintelligent who need it the most. In 75 per cent of the cases we really don't know how to make the sterile fertile. We don't know how to curb the soul searing and health wrecking traffic of the criminal abortionist. There are many similar gaps in our knowledge of fundamentals in this field.

What can we do to achieve the aim of maximum reproductive efficiency in the United States. The post-war world will impose upon us a multitude of responsibilities which will require a large, efficient population with both brains and brawn.

First, we must unshackle medicine from the church's dominaton.

We must place the social problems of human reproduction in their proper setting, divorced from religion, and an integral part of modern science.

Second, the weight of public opinion must convince existing Government health agencies that the social problems of reproduction have no time fuses attached which may cause shattering political explosions. Public opinion alone can remove the fuse pins.

Third, we must do more fact finding and less speculating. We need basic investigations of the type that Eastman carried out at the Johns Hopkins in Baltimore, and Yurashalmy on births from New York State. These investigators demonstrated independently that the risk to both the mother and baby rises sharply after the eighth birth. There are many similar problems still unplumbed.

Fourth, initiate a program of selective pregnancy. Encourage women to have children while they are still young and fertile. Bring pressure to bear on the small-familied upper classes to make them realize their privileged responsibility to have many children. Select those who are eugenically unsound and offer them the means to avoid bringing tainted offspring into the world. (Notice, I said offer, not compel, for this is a free America.)

Fifth, extend the obstetric care so well initiated by the Children's Bureau, so that in the ideal, every pregnant woman will have the best care medicine can offer, irrespective of pocket book or social status. This may entail some socialization of medical care; well and good if such a program will yield superior results to private medical care. In this case, the means of achievement is unimportant.

We have journeyed a long way from the medicine of yesterday to the medicine of tomorrow. In planning and preparing for the medicine of the future let us do it in the spirit of Oliver Wendell Holmes: logically, frankly and without rancor.

THE TREND OF THE BIRTH RATE YESTERDAY, TODAY AND TOMORROW*

Louis I. Dublin, Ph.D.

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this occasion, I propose to consider the subject of births in terms of the meaning they have for our country. We must remember that the number and succession of births determine, in large measure, the composition of the population and the composition of the population in turn determines the character of our economy and the style of our very national life. If, in war-torn France and Germany the births of 1917 dropped to one-half their usual level, then in 1937, the number of young men and women at age 20 were proportionately reduced. This meant that in 1937 there were so many less marriages and a little later so many less births. Thus, a new foundation was laid for gaps in the population of the next generation. Evidently, then, births have a particular significance for the nation both in peace and in war, a fact that must ever be in the mind of the statesman planning the future welfare of his country. All of you must have read, within the week, the remarkable speech made at Nottingham by Herbert Morrison, the Home Sceretary for England who, surveying the situation in his country, came to the matured conclusion that the size of the average British family must be increased 25 per cent after the war period, not only to maintain the population at its present level but, more important, to lay the foundations for a social order that will provide better standards of living for the nation. This topic is a live issue today as we celebrate the Twentyfifth Anniversary of the founding of the Maternity Center Association, which has made a truly great contribution toward safeguarding maternity and the American family.

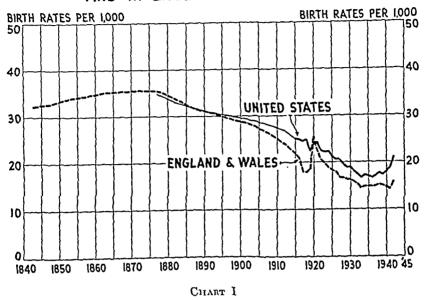
Let me first call your attention to a fundamental consideration which surrounds any discussion of births and birth rates at the present time. The birth rate in the last century underwent a revolutionary change, even greater than the remarkable reduction in the death rate. I presume

^{*} Address presented before Conference on Maternal Health and Child Welfare, Hotel Roosevelt, February 19, 1943.

that until the beginning of the 19th century, only very slight changes occurred in the level of birth rates and of death rates throughout human history. Both of these biological phenomena were subject to natural causes and very little to man's control. In the first half of the 19th century, however, death rates began to topple as men learned how to gain control over the environment and the sources of infections. The revolution in birth rates which began at about the same time, was brought about largely by man's winning control over reproduction. The perfection of the methods of contraception and their spread over the whole civilized world are of the same order of importance as the extraordinary advances in saving human life. Together, these two changes constitute, I believe, the most significant events of the last century. Bernard Shaw once remarked that the discovery and spread of contraception was the most important single event in human history. For, the control of the birth rate and of the death rate gives man the power to determine not only the size but the character of the nation. We must not think of birth rates and death rates as mere statistics but as the fundamental basis on which our society is built. My purpose today, then, is to analyze briefly what has happened during the last century, particularly in birth rates, so that you may understand better the forces which are now at work and which may operate in the immediate future. By learning how to control these forces, we can more intelligently adjust our affairs to accomplish the best organization of our society.

Follow with me what has happened to the birth rate during the last century. About a hundred years ago, the annual birth rate in England and Wales fluctuated around a level of 35 per 1,000 of population. There is good evidence that the birth rates in the United States were, broadly speaking, of the same order. We know that the figure in 1875 was about 35 per 1,000 in both countries, as is indicated in Chart I. In some agricultural countries, and particularly in certain backward areas, the rates were higher, reaching in excess of 40 per 1,000. These high levels were fairly well maintained until the early eighties. Beginning at about that time, a decline set in, first gradual and later much more rapid in its course. By 1900, the figure for England and Wales was already under 30 per 1,000; by 1920, between 20 and 25, and by 1930, well under 20. In our own country, we scraped bottom during the depression year 1933 when the birth rate was only 16.6 per 1,000, or less than half the level of 1880, about fifty years earlier.

BIRTH RATES IN THE UNITED STATES AND IN ENGLAND AND WALES



You will notice that I have not referred to the marked diminution in the birth rate which occurred during the period of the first World War. That was a temporary phenomenon superimposed upon a long-time-trend. The chart indicates that the figures immediately swung up again in 1920 from the very low figures of 1917 and 1918 in England and the United States, respectively. In England, the low figures of the depression years have shown little or no recovery. In our own country, there was an upswing beginning in 1933 which has continued almost without interruption since then, and last year the birth rate stood at 21 per 1,000, the highest since 1925.

Broadly speaking then, the course of the birth rate over the last century has been one of marked decline. I may say also that this decline would clearly have been fatal to our country and to other countries of the civilized world had it not been accompanied by a very marked decline in the death rate as well. Death rates of 30 per 1,000 and over were not uncommon 100 years ago. Such death rates combined with modern birth rates, would send our population shrinking to one-half in about two generations; and to one-quarter, that is to less than 35 million people, in a little more than a century.

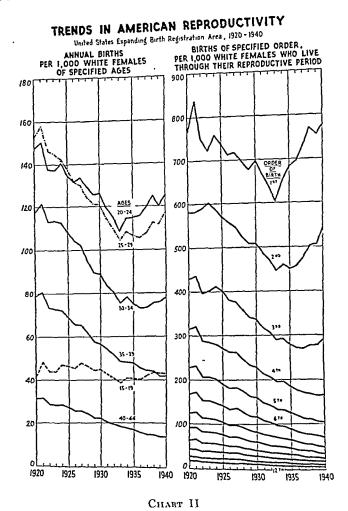
Now let us look at the matter the other way around. Birth rates

such as those of 100 years ago associated with the death rate of today would involve very large increases in population. It would mean a population of 275 millions in 35 years and of 550 millions in 70 years. This would bring back the bogie of over-population with a vengeance. Fortunately, we are not confronted with either of these two terrifying alternatives, either of national suicide or of disrupting over-population. We are now in the rather favorable position in which our birth rate and death rate are in excellent balance. One hundred years ago, many had to be born that a few might survive. The average number of children in the American family of that day was about six. Today, we enjoy an economy of lives and a greatly diminished burden on mothers; for an average family of three children is now adequate to maintain our population. I need hardly point out that with the smaller families of today, parents can take much better care of their children and the whole family economy can be maintained at a much higher level. Altogether, we can look upon the decline in both the birth rate and in the death rate to their present levels as unmitigated blessings.

Quite recently, as I have told you, we have seen a reversal in the trend, a rise in our birth rate. You may very properly ask what is the significance of this. Does it presage a continued upward trend? I do not see any evidence that it is more than a temporary departure, reflecting the improvement of economic conditions since the depth of the depression years, and, more particularly, the effect of our defense preparations culminating in our actual entry into the war.

The higher birth rates of the last few years stem very largely from the marked increase in the marriage rate. The continued depression and consequent unemployment of the early 30's operated to delay many marriages. The economic revival resulted in the realization of these delayed marriages, with the consequent increase in the number of births in the years immediately following. The prospect of military service likewise operated even before our entry into the war as an occasion for hastening many contemplated marriages. The outbreak of the war in December 1941 led to a flood of marriages, and contributed largely to the very marked upswing in births the following September and October. The war situation has stimulated the increase in the birth rate.

It must be obvious, however, that this upward trend in the number of births cannot continue. A turning point will soon be reached. Our increasing participation in the war and the protracted absence of our



men, even of fathers of families, in foreign countries, will result, in this war as in the last, in reducing the birth rate markedly, to figures as low as or even lower than that of 1933.

These conclusions are supported by the fact that the recent rise in the number of births is found on examination to be concentrated among young married people, as is indicated in Chart II. As you will see from the left-hand panel, the increase in births, since 1933, is almost altogether limited to women between the ages of twenty and twentynine. If you will look at the right-hand panel, you will see the facts presented in a somewhat different fashion. This panel shows the birth rates by order of birth. You will notice that the recent increase is particularly marked among first births. It is less marked among second

births, while births of fourth and higher orders have continued to decline. All this is of a piece with the supposition that we are dealing with a merely temporary increase in the birth rate, arising from relatively recent marriages, a rise in which the older women have taken no part at all. This temporary increase in the births of first and second children does not materially change the prevailing picture of the tendency toward a small American family.

Another important question which I would like to consider with you today is what our attitude should be toward birth rates and the size of the family in the near future. That we may better understand the nature of this problem I must first clarify what has been happening in our country and in other civilized countries during the last two or three decades. As you know, there was, even at the time of the lowest levels of the birth rate, a sizable margin of births over deaths. To all appearances, the population was still increasing in numbers. Thus, in 1933, the birth rate of 16.6 per 1,000 exceeded the death rate of 10.7 per 1,000 by 5.9. The natural increase for the year in our population was about 750,000 people. That certainly did not seem like a dangerous situation and certainly not one that called for great concern over the future of our numbers. And yet there was room for considerable concern. That is because this obvious and apparently simple approach to a consideration of population growth is thoroughly misleading. The margin of births over deaths in any one year is not at all an indication of what is happening with reference to the maintenance of the population over a generation or more. There are certain fortuitous circumstances which cloud the picture. Thus, in a nation where there is a high proportion of people at the reproductive ages, as in our country, the birth rate will appear high even under conditions when the fertility is not sufficient to balance mortality. Exactly that has been happening here and in most other civilized countries during the last thirty or forty years.

Birth rates, as I showed you before, have been steadily declining. The immediate result is to give the present population a larger proportion of persons at the reproductive ages than the current fertility and mortality would in the long run yield. We inherit these people from the high birth rates of the previous generation and the result is to give a totally false picture of what is currently happening. Once this conception was clarified, and the proper analysis was made, we saw at once how different the actual situation of population maintenance was from

NET REPRODUCTION RATES, UNITED STATES, 35-40

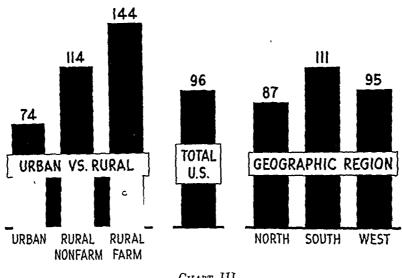


CHART III

the surface appearance of the current birth rates and death rates. Students in this country and abroad became truly excited over what was happening. On analysis of the true rates of natural increase corrected for the temporarily large concentration of the population in the reproductive ages, we found that in our country, which was still increasing at the figures I just pointed out, we were actually not maintaining ourselves over the generations. In fact, we found that a continuation of our prevailing fertility would mean a declining population in the next generation. This was actually the situation in 1933, when the net reproduction rate was 94 per cent.

Even in the five years between 1935 and 1940, when birth rates were on the rise, the net reproduction rate in the United States was only 96 per cent (Chart III). In other words, we were on the way to a decline, even if slowly. In certain European countries, the situation was much more acute. In England and Wales, for example, the net reproduction rates were as low as 73 per cent in 1933, and the statesmen of that country, once the figures were brought home to them, were much disturbed by the prospects of an impending slump in population. One can very well understand how in the light of the losses sustained in the current war, Mr. Morrison emphasized the necessity of raising the birth rate of England 25 per cent. In Germany, before the advent of the Nazi regime, birth rates declined to their lowest levels, reflecting the depressed state of mind of the entire nation. The reproduction ratio was even lower than that in England, namely 70 per cent. The situation in France was equally unsatisfactory, and you can very well understand, therefore, the immediate concern of the governments in these countries with the problem of the maintenance of their populations, and why they took particular pains to bolster up their birth rates, utilizing every conceivable method of increasing the number of children born.

I hold no brief for the procedures which Mussolini and Hitler followed in increasing their populations, and certainly none for the motives which inspired the various moves that they made. The significance for us of their several efforts lies in the fact that there is grave need for a matured population policy in our country. Any such policy must take account of the more detailed analysis of the prewar reproductive rate for the country. The figures, computed separately for the cities and for the rural areas, present a striking contrast. Thus, in the period 1935-1940, the urban population showed a net reproduction rate of only 74 per cent, whereas the population on the farms showed a net reproduction rate of 144 per cent, that is 44 per cent in excess of what was necessary for maintenance. If our whole nation were an urban population, we would according to these prewar conditions be declining by one quarter in each successive generation. On the other hand, on the farms, the population would increase by almost a half in each generation. That is obviously not a healthy condition.

The farms and the rural areas of our country are the reservoirs of much of our future population and they are making good the deficiencies in our reproduction in the cities. If life on the farms were as favorable as it should be, if education and other facilities of civilized living were on a sufficiently high level, one might accept that solution with little misgiving. But, as everyone knows, conditions of life on many of our farms are substandard. Educational facilities are far from what they should be. Large numbers of our rural population live under extremely difficult economic deprivations. Even their nutrition has been found to be defective, as is indicated by the strikingly high rates of defect and deferment in the draft among the recruits from many of the rural areas. The children growing up on the farm do not have the medical care nor do the enjoy a great many other facilities which are necessary to

bring up a vigorous, trained and effective population.

Much the same story appears when we contrast the geographic areas of the country (Chart III). The Northern States are 13 per cent in defect; the Western States 5 per cent in defect and the South has a favorable margin of 11 per cent. Similar or even more striking differentials have been found with reference to the net reproduction rates of certain groups of the population, specifically in relation to education and economic condition. These studies indicate that reproduction rates are uniformly high among economically and educationally less favorable groups and correspondingly deficient in those living under higher standards. It is clear, therefore, that if we are still on the safe side of the population ledger, it is only by a narrow margin. Evidence of a threat of decreasing population is not a mere abstraction but a very real fact. For one thing, we see already a constantly decreasing number of children in our schools. Even in our own city this annual decrement has been of the order of 25,000, and this is a countrywide phenomenon.

The differentials of fertility are not indicative of a healthy national policy. There is room, therefore, for much careful thinking and for the education of the people to realize what is actually at stake. This is not the occasion for a prolonged or a definitive outline of a scheme. But a few points I would make:

First, that under present conditions of mortality, it is necessary for the average number of children per family to be at least 3; that less than that number threatens a dangerous decline in our population.

Some years ago I made a similar address, which is worth recalling on this occasion. Because of the higher mortality then prevailing, the average number of children required to maintain the population was 5.1 per family. Of course, everyone in my audience understood what this figure meant except some of the newspaper men present. In their confusion, they assumed that I advocated an average family of 5.1 and one ingenious editor interpreted this family of 5.1 as follows: Four children, one mother and .1 represented father. Now that the decimal fraction has been altogether removed, I hope no one will be tempted to interpret this as the complete elimination of father.

Secondly, we should profit from the experience of other nations, and develop a sensible population policy to minimize the differentials which now make the development of our population haphazard and, in the estimation of some competent students of population, actually

dysgenic. Here is a field for constructive thinking. We must assume that contraceptive knowledge will become increasingly available to all classes. It therefore becomes more than ever important to encourage voluntary parenthood. This must be done by improving the living standards of the community. We have much to learn from little Sweden which has attacked this very problem in a constructive fashion. There, the program to encourage parenthood was made a part of a broad social welfare scheme. In our own country, much will depend on the solution of our fundamental economic problems after the war to assure stable employment at good wages for the great mass of our people. Proposals for more adequate social security will undoubtedly play a part in our future national organization. All of these measures should contribute to a more willing assumption of the obligation of parenthood. The aim of our policy should be to maintain our present population levels but with a more equitable participation of all healthy groups of the people. In carrying out this program, I can see much room for the continued services of your organization. Over the last twenty-five years, the Maternity Center Association has helped to make maternity safe and has very largely succeeded in achieving this much desired result. In the next quarter century, it should be a very useful agent in stimulating thought with regard to the larger problems of family welfare on which I have just barely touched.

THE ROLE OF ARTIFICIAL INSEMINATION IN THE TREATMENT OF HUMAN STERILITY*

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T if tion, test-tube babies, implies something magical. It connotes a laboratory in the spirit of Dr. Kildare, with white-coated, bespectacled doctors mysteriously brewing babies from ectoplasm. Obviously this is not true.

Actually, artificial insemination supplies a relatively new and scientific treatment in certain types of human sterility. This afternoon, I hope to demonstrate the limitations, as well as the indications, for this much applauded cure.

Historically, artificial insemination is one of those rare medical entities which cannot be traced back to Hippocrates. Furthermore, no reference exists to it among preliterate peoples. In fact its first human application was made a scant century and a half ago.²

A poorly documented legend traces the source of the procedure to the fourteenth century. In 1322, an Arab sheik, made jealous by the superior horsestesh of a rival, sent some men in the stealth of night to inseminate the mares of the enemy with semen collected from a scrub stallion.³

In 1680, Jan Swammerdam, physician, mystic and natural philosopher of Leyden, reported unsuccessful attempts to fecundate artificially the eggs of fish, an experiment accomplished by Jacobi twenty years later. The first scientist to concentrate on the problem was the swarthy-skinned, brilliant-eyed, magnetic Abbé Lazzaro Spallanzani, who began his career by taking Holy Orders, and at twenty-five turned to a secular professorship in Greek, logic and mathematics. His real bent, however, was for biology, and at thirty-nine he became professor of Natural Philosophy at Pavia. When fifty years old, he artificially fertilized an insect,

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then an amphibian and finally a dog. Spallanzani published a description of the latter experiment in 1780.3

"I chose a bitch spaniel of moderate size which had before had whelps. Suspecting, from certain appearances, that she would soon be in heat, I confined her in an apartment, where she continued a long time, as will be seen below. For greater security, that she might never be let loose, I fed her myself, and kept the key the whole time. On the thirteenth day she began to show evident signs of being in heat; the external parts of generation were tumid, and a thin stream of blood flowed from them. On the twenty-third day she seemed fit for the admission of the male, and I attempted to fecundate her artificially in the following manner. A young dog, of the same breed, furnished me by a spontaneous emission, with nineteen grains of seed, which were immediately injected into the matrix, by means of a small syringe introduced into the vagina. As the natural heat of the seed of animals of warm blood may be a condition necessary to render fecundation efficacious, I had taken care to give the syringe the degree of heat which man and dogs are found to possess, which is about 30°. Two days after the injection, the bitch went off her heat, and in twenty days her belly appeared swollen, which induced me to set her at liberty on the twenty-sixth. Meanwhile the swelling of the belly increased; and sixty-two days after the injection of the seed, the bitch brought forth three lively whelps, two male and one female, resembling in colour and shape not the bitch only, but the dog also from whom the seed had been taken. Thus did I succeed in fecundating this quadruped; and I can truly say, that I never received greater pleasure upon any occasion, since I first cultivated experimental philosophy."

It is likely that the great John Hunter ran across Spallanzani's account, for the English translation which I have just read was published in London in 1784. This diligent, brilliant and ingenious man, with his own flare for natural philosophy, was probably greatly impressed by the account of his Italian colleague and ill-bided the time until he would chance upon a suitable human case in which to try Spallanzani's procedure. Such a case appeared about 1790, though it is impossible to fix the exact date since Hunter, himself, did not publish it. Everard Home, his nephew, simply refers to it in an article on Hermaphrodites in the 1799 Philosophical Transactions of London. Home states that "Spallanzani's experiments on this subject, on animals, were

made several years after this proposal of Mr. Hunter's had been attended with success." However, most authorities believe that Spallanzani's experiments antedated Hunter's.

Hunter was consulted by a man rendered sterile from a complete hypospadias. Home writes, "He advised that the husband should be prepared with a syringe fitted for the purpose, previously warmed; and that, immediately after the emission had taken place, it should be taken up by the syringe, and injected into the vagina, while the female organs were still under the influence of the coitus, and in the proper state for receiving the semen. This experiment was actually made, and the wife proved with child. On a subject of this kind it is proper to speak with caution; but, from all the attending circumstances, no doubt was entertained by Mr. Hunter, or the husband, that the impregnation was entirely the effect of the experiment." One would infer from this terse account that the husband served as both donor and innoculating technician. It is also noteworthy that the first successful human case followed intravaginal, and not intrauterine, injection.

The third great name associated with artificial insemination is that of J. Marion Sims, founder of the Woman's Hospital, originator of the duck-bill speculum, and successful surgeon for cross-eyes, club-feet and vesico-vaginal fistulae. In his work on "Uterine Surgery," published in 1866, he reports fifty-five artificial inseminations on six different patients with one pregnancy resulting. In his usual careful and accurate manner Sims describes his technique in detail.

In each instance the husband was the donor, in fact, I believe the thought of any other source for the semen would have shocked so good and pious a Southern doctor. The semen was kept meticulously at 98° F., and in his early experiments, three minims were injected into the uterine cavity. Later the quantity was reduced to half a minim since more produced "severe uterine colic." In referring to even this small amount he sagely wrote: "Indeed, I have no idea that this quantity ever gets into the cavity of the uterus in Nature's own way," a conjecture which many of us would do well to reiterate. Sims describes the case of this twenty-eight year old patient in detail. She had been married nine years without issue, her uterus was retroposed, the cervical canal "contracted" and the vagina unable to retain semen. After holding the uterus forward with a pessary, he introduced the semen into the uterine cavity on ten occasions, twice just before menstruation, and eight times from

two to seven days after it had ceased. Unfortunately, after becoming pregnant, the poor lady miscarried from the combined effects of a 'fall and a fright'." Sims concludes, "I have related this case minutely, because I presume it is the first and only authentic case in which artificial fertilization has been successful in the human species; and because it furnished about the sum and substance of my knowledge on the subject which may be of any possible service as a guide to future observers, who may have the curiosity, leisure, courage and perseverance to experiment further in this direction. . . . I have given up the practice altogether and do not expect to return to it again."

Artificial insemination received scant attention until the animal doctors showed the human doctors its great possibilities. The first stanch advocate in animal husbandry was the Russian worker, E. I. Iwanoff, who published his distinguished monograph in 1907. Since this date it has played an increasingly important role in animal husbandry. Hundreds of horses, cattle, pigs and sheep are conceived by it each year in the Soviet Union. The Russian government has blooded males quartered throughout the agrarian regions in scores of animal breeding stations, and the peasants are encouraged to bring their mares, cows, ewes and sows for impregnation. In this way Russia improves the quality of her livestock, for by artificial insemination one blooded stallion may begat a half-dozen or more colts at one service. According to Kersin, as many as 15,000 ewes were inseminated by one ram in the breeding season of 1936, and more than 1,000 cows by one bull. The average proportion of conceptions in the ewes was 96.6 per cent, and in the cows 93.7 per cent. The Animal Husbandry Division of the United States Department of Agriculture has become greatly interested in this topic and their seventy-page circular written by Lambert and McKenzie is at once a scholarly and an amazing survey of the theory and practice of artificial insemination in the horse, cow, sheep, pig, dog, fox, rabbit, chicken and turkey.6

Physicians to the human race, in comparison with physicians to dumb brutes, are leagues behind in both the scientific investigation and the successful practice of artificial insemination. To be sure, we are trammeled by conventions, moral codes and frailties of human character, which never hinder the stockbreeder.

In the last three decades artificial insemination has become increasingly important in the solution of the problems of human sterility. By

1928 Engelman was able to collect 185 attempts from the world literature, and since then more than a score of papers have been published, several reporting at least ten cases.

Three of the largest human series are those of Schorohowa,⁷ reported in 1927, of Cary¹ in 1940, and of Schultze⁸ in 1941. Schorohowa reports fifty cases with twenty-two successes, Cary thirty-seven, with fifteen pregnancies, and Schultze one hundred and two attempts with fifteen successful. Schorohowa's report, the most optimistic, is far from convincing. The figures do not tally and there is a disturbing lack of detail in such matters as the number of injections performed in each case. Furthermore, half of his successful results appear to have followed injection during the most sterile phase of the cycle, within one to three days before an expected menses. Schultze's and Cary's papers, on the other hand, are quite detailed and accurate.

We have purposely excluded from our references to the literature, the astounding and dramatic paper of Frances I. Seymour and Alfred Koerner. Their contribution from the National Research Foundation for Eugenic Alleviation of Sterility, Inc., was published in the authoritative Journal of the American Medical Association in June 1941. I have not had the opportunity of meeting or corresponding with either Dr. Seymour or her co-author, Dr. Koerner, so that my candid analysis of their publication will be utterly impersonal. I propose to submit the paper to the same cruel scrutiny that I hope they would give mine; the kind of careful consideration true scientists find most flattering.

Their paper is based upon a questionnaire sent to 30,000 United States physicians who might conceivably be interested in artificial insemination. The result was "that 9,489 women had achieved at least one pregnancy by this method." In the words of Dr. Clair Folsome, director of the National Committee on Maternal Health, who is in the process of publishing a critical Review of the Status of Artificial Insemination, "This number is arresting when one considers that it is approximately twenty-one times greater than that reported in the entire medical literature during the previous four decades."

Another remarkable item in Seymour and Koerner's paper is the fact that "more than 97 per cent of all the pregnancies resulting from artificial insemination terminated in living, normal babies." This means that there was less than a 3 per cent pregnancy wastage from the combined effects of spontaneous abortion, intra-uterine death, and birth trauma, plus the congenital malformations. When pregnancies are achieved per via naturalis at least 10 per cent are aborted, 1 per cent die in utero, 3 per cent are lost through birth trauma and prematurity, and at least another half per cent have serious malformations. This totals a minimal, ordinary pregnancy wastage of 14.5 per cent, which is 500 per cent more than the Seymour-Koerner series.

Dr. L. B. Tuckerman, a physicist for the Bureau of Standards with wide biological interests and keen mathematical insight, has called Dr. Folsome's and my attention to some of the arithmetical inconsistencies in the Seymour-Koerner paper. Seymour and Koerner state that "9,489 women achieved at least one pregnancy" and "that in 1,357 patients more than one pregnancy was effected by this means," which would yield a minimum of 10,846 pregnancies. If we deduct 325 for the 3 per cent loss from their pregnancy wastage, it leaves 10,521 viable, normal children. Yet the authors state that "the grand total of children sired by this method and here reported is nearly 9,500." What happened to more than one thousand and twenty-one babies that must have been piped away by some mathematical pied-piper?

Furthermore, there is no mention of even one multiple birth among the 10,846 women who achieved artificial impregnation. If the 125 multiple pregnancies anticipated did occur, then the mathematical pied-piper's family would have to grow apace.

Then too, the sex ratio of their artificial insemination children is at least exceptional, 160 males to 100 females, in place of the usual 106:100, a ten to one increase in the normal excess of males. The sex ratio when the husband's semen was used was slightly greater than when a donor's semen was employed. Accepting the Seymour and Koerner data, Dr. S. Kardimon, 11 in the October issue of Urologic and Cutaneous Review, ingeniously explains the greater male potentialities of the husband's versus a donor's semen. He writes that when "the husband's semen is being used the patient feels self-assured and contented; this results in the cervical secretion flowing more freely, thus providing a more alkaline medium which favors . . . males in an 8:5 ratio. When a donor's semen is used, the patient feels embarrassed and timid with the result that the flow of cervical secretion is somewhat hampered, thus providing a less alkaline medium, and . . . a less chance for boys to be conceived, a ratio of 7:5 girls." Can one explain the unusually high sex ratio of the whole Seymour-Koerner series on Kardimon's naive hypothesis, greater contentment by the wife during artificial insemination than during normal coitus? If so, we shall have to revise the male ego and many of the basic tenets of the psychotherapeutist.

The final inexplicable fact in the Seymour-Koerner publication to which I should like to call your attention, is the curve which they publish showing the number of inseminations necessary, in the individual patient, to achieve conception. Forty-five per cent of the 9,489 pregnancies occurred at the twelfth attempt. Twelve was a curiously lucky number in their series; bearing for them a great contrast in good fortune to "Big Joe" in dice. Furthermore, 85 per cent of the conceptions occurred after nine inseminations had been done and before sixteen were tried. The most difficult thing for me to understand in the whole paper is that only 490 pregnancies (5 per cent) occurred when eight or less inseminations were used. That is, only one patient in twenty conceived before the ninth attempt. This is in direct contrast to my own experience, and that of other workers in this field.

I believe I have justified my temporary exclusion of the Seymour-Koerner paper from the accurate, scientific publications in this field, and I shall continue to exclude it until the authors satisfy the doubts that Folsome, Tuckerman, Cook, editor of the Journal of Heredity, Dr. Robert L. Dickinson, myself and others have expressed. The moral of this tale, and such a tale must have a moral, is that editors of scientific journals should refuse the publication of such dramatic and unprecedented material unless well-documented by protocols and bibliography; neither of which Seymour and Koerner's paper possesses. Their paper is widely quoted and blindly believed, for great power has the printed word!

A consideration of the role of artificial insemination in the treatment of human sterility brings to the fore several matters for frank discussion. In the first place, when should artificial insemination be used? In the second place, what technique is to be followed? In the third place, how should a donor be selected? In the fourth place, what are the moral and legal aspects? Several of these topics are highly controversial.

INDICATIONS AND TECHNIQUE

The indications for artificial insemination may be divided into three main groups: In group A are those cases in which intravaginal coitus

between two fertile individuals is impossible because of mechanical factors: impotence, hypospadias, vaginismus, tumors or excessive obesity. Group B is an all inclusive group made up of chronically sterile couples who finally qualify for this-the vaunted sterility treatment of last resort. Conditions admitting a couple to Group B are legion, but I shall content myself in simply listing those printed in the three papers of Schorohowa,7 Schultze8 and Cary.1 They are: anteflexed uterus with conical cervix, retroposed uterus with conical cervix, uncomplicated anteflexion, uncomplicated retroflexion, hypoplasia of the uterus, relaxed perineal body, salpingo-oöphoritis, endometritis, enlarged uterus, cervical abnormalities: such as stenosis, endocervicitis and hypertrophy of the cervical mucous membrane, and finally a subnormal semen. In the third group, group C, are included only those cases in which the husband is sterile and the wife apparently fertile, or in which the husband has cacogenic hereditary characters which make a child sired by him illadvised. Of course in Group C only semen from an unrelated donor is employed.

It is appropriate at this point to inquire into what percentage of sterile matings are due to the male, and in which of these his condition is hopeless enough to justify heterologous artificial insemination. A thorough discussion of this would require an afternoon in itself; the criteria of a defective semen, the consistency of the sperm picture in the same individual, the chance for restoration to sperm health under a therapeutic regimen, etc.

To get a rough idea of the maximum percentage of cases in which heterologous artificial insemination might be indicated, I have analyzed the sperm counts of 208 successive semen specimens sent to the laboratory at the Johns Hopkins. I shall consider only the count because it is the simplest single factor to determine; it can be done most accurately; and usually when the sperm number is normal, other factors in the semen picture are likely to be normal, and when deficient, other elements are likely to be deficient as well. Dr. L. B. Shettles, of the department of obstetrics, has been carrying on studies in sperm physiology for a number of years under the auspices of the National Committee of Maternal Health, and the 208 specimens referred to are those of sterile couples sent to his laboratory for routine analysis. All the counts were made by Dr. Shettles. In 128, or 62 per cent, the sperm count was normal, i.e., more than sixty million per cubic centimeter;

in 16 per cent it was between thirty and sixty million; in 12 per cent between ten and thirty million; in 7.5 per cent less than ten million; and in 2.5 per cent there was a complete absence of spermatozooa. In my opinion, if the 22 per cent whose counts were less than thirty million continue to show this same low figure in repeated specimens despite the benefit of time and therapy, their physicians might justifiably consider the wisdom of a heterologous insemination. Certainly, without much question, the 10 per cent with less than ten million, or no spermatozooa, would justify it.

I can find no definite statement as to who first employed semen from an unrelated donor. Beardsley¹² used it in 1921 and it was probably used much earlier. Israel differentiates insemination with the husband's specimen from that with a donor's specimen by designating the former homologous artificial insemination and the latter, heterologous.

Dr. Max Huhner¹³ believes that no matter what indication exists the Huhner test should always be performed before resorting to artificial insemination. He states that he has seen many cases in both sexes, including male impotence, where it was thought that the spermatozooa could not gain access to the cervical canal, and yet upon post-coital examination, there they were. And if any motile spermatozooa are found within the cervix, Dr. Huhner considers them a contraindication to the necessity for artificial insemination.

Schultze used artificial insemination in the treatment of 102 out of 2,000 sterility cases (5 per cent), while Schorohowa employed it fifty times in a series of 586 cases (9 per cent).

All physicians accept the value of artificial insemination in the treatment of groups A and C, that is when intravaginal coitus is impossible or when the semen of a fertile donor is substituted for the sterile or cacogenic semen of the husband.

I have had two patients in group A. The husbands were incapable of coitus but ejaculation of semen was possible by masturbation. In each, pregnancy occurred during the second course of intravaginal injections of the husband's semen. Cary¹ in his series of thirty-seven artificial inseminations, had one case of hypospadias in which treatment was successful. Schultze⁸ had forty-eight couples for whom coitus was impossible. All the women were treated by the intrauterine injection of the husband's semen, and only six became pregnant. As I shall point out later, his low incidence of success in the A group may well have been

because his patients received intrauterine injections, while Cary's and mine were inseminated intracervically or intravaginally.

I have had thirty-four cases in group C, which constitutes appar-

I have had thirty-four cases in group C, which constitutes apparently-fertile women who receive injections with semen collected from unrelated fertile donors. In eighteen cases pregnancy resulted; five women are still under treatment and in eleven cases one or several treatments failed and further attempts have been discontinued. Cary reports nineteen such cases with eleven pregnancies. If one eliminates my five cases which are under current treatment, the combined figures from Cary's series and my own total forty-eight cases with twenty-nine pregnancies (60 per cent).

It seems pertinent at this point to say a word about artificial insemination with spermatozoa aspirated from the testicle by puncture of men whose epididymides or vasa deferentia are occluded. After Iwanoff had demonstrated the success of this procedure in the horse it was attempted in human cases. The testicles of the sterile husband are needled in several places, and after many punctures a few drops of secretion are aspirated. Two cc. of sterile salt or Locke's solution is then sucked up into the syringe and mixed with the aspirated spermatozoa. The diluted spermatozoa are immediately injected into the wife at a favorable phase of her menstrual cycle. I myself have had no experience with the procedure. Schultze attempted it in four cases with failure in all. He states that no authentic successful case has yet been reported. Dr. Huhner¹³ states that he was the first to try this procedure, but that all of his numerous attempts failed. Dr. Huhner calls attention to the fact that Kenneth Walker in his book, Male Disorders of Sex, published in London, 1930, reports a successful case by C. H. Mills, an English surgeon. Rohleder reported one pregnancy in a series of seven patients, but he himself suspected that the success may have been due to extramural activities on the part of the wife.8 Neither Young nor Cabot index this procedure in their textbooks of urology, and Hinman dismisses the matter with the generality that "it has been tried successfully a few times."

Young, however, gives a detailed description of a somewhat similar procedure in his book on congenital abnormalities. He exposed the testicles, cut across distended tubules of the globus major, aspirated the spermatozoa and injected an estimated 200,000,000 into the uterus of the wife. This rather formidable procedure was done twice on the same patient without success. Young states that Hagner had also tried artifi-

cial insemination from aspiration of the epididymis and failed.

The B group is the group about which there is much difference of opinion with regard to the therapeutic value of artificial insemination. These are the cases in which no cause for infertility is found in either partner, or at the most some non-sterilizing abnormality not directly concerned with the delivery or reception of the semen.

From the purely physiologic point of view, artificial insemination ordinarily has no advantage over coitus in treating sterility of undetermined origin, and I am convinced that it is also of little value in sterility due to a subnormal semen. If the spermatozoa are so pathologic that they need "a 3 inch boost" on their 6 inch journey, I believe they are likely to be sterile when face to face with a fertile egg.

I performed intravaginal or intracervical inseminations in seven group B cases, a total of thirty-three injections, with no success. In two, the husband's semen was defective and in the other five cases, there was some cervical abnormality in the wife. Incidentally, one of the latter group reports an early pregnancy with normal coitus following cervical dilatation and thyroid and Vitamin E therapy. Schultze employed artificial insemination with the husband's semen in forty-seven cases of this B group. Twenty-eight women had hypoplasia of the uterus and four became pregnant but all aborted. Nineteen had cervical lesions and three became pregnant. Cary reports fourteen failures and three successes in this group-in one case the semen was subnormal and in two, the women had acute anteflexions. Together, Schultze and Cary had sixty-four cases in group B with ten pregnancies (16 per cent). It is important to point out that these authors performed intrauterine inseminations. If one is going to treat the problem of subnormal fertility by artificial insemination with the husband's semen, I believe that intrauterine insemination offers greater likelihood of success than the intravaginal or intracervical method, since in reality these have been employed for years through normal coitus. On the other hand, if artificial insemination is simply a substitute for coitus in instances in which it is physically or morally impossible, the intravaginal and intracervical routes are greatly superior.

Many authors make vaginal-cervical insemination absurdly complex. In group C cases, that is, in instances, in which the semen of a fertile donor has been substituted for that of the sterile husband, I have had 62 per cent success, despite the use of a very simple technique. The

specimen is collected by masturbation into a dry, clean, wide-necked bottle or drinking glass, no attempt being made to collect it sterilely. There is no need for hurry. If the material is to be injected within two hours of ejaculation it may be kept at room temperature. If a longer period of time is to elapse, it is best kept in a corked bottle or test tube at 6° C.

The animal husbandry group has carried out some fascinating experiments on the effect of the age of the semen specimen on the success of artificial insemination. Walton and Prawochenski shipped ram semen from England to Poland and had successful impregnations twenty-seven hours after collection. Winters in this country reported two successful impregnations with ram semen that had been kept in the laboratory ice box for six days. Gunn reported as great a percentage of impregnations in ewes with semen stored for twenty-eight hours at 6° C. as with fresh semen. The United States Department of Agriculture shipped bull semen to Argentina and had at least one successful impregnation. The time elapsed from collection to impregnation was seven days.⁶ As far as I know, similar experiments have not been carried out for man, and they would form an important investigative project for a research sterility clinic. Several of my successful results were accomplished with specimens at least two hours old.

The animal husbandry group has shown that the best place to deposit the semen varies with the species. In general it should follow the pattern of normal coitus. For example, in the cow it should be inserted 1 to 2 cm. within the cervix, while in the sow it should be introduced directly into the uterus. The amount of semen necessary for successful artificial insemination also varies from species to species. In the chicken, for instance, 0.1 cc. is sufficient, while in the sow from 100 to 200 cc. is necessary, depending on the size of the animal. Here again there are no similar scientific data for the human.

The date for insemination is carefully selected on the basis of the woman's menstrual data. If the cycle is 28 days, the procedure in the first month is to select days 11 and 15, considering the day of the onset of the menses as day one. If the treatment fails the first month, the next month days 10 and 14 are chosen, the next month days 12 and 16, and so on, varying the days back and forth within the confines of the fertile period. If the patient's average menstrual cycle is more than 28 days, for example, 31 days, I add 3 days for my initial attempt to the

usual eleventh and fifteenth days, doing inseminations on days 14 and 18. If the cycle is 25 days, I subtract three, using days 8 and 12 for my first attempt. The watery, transparent character of the cervical mucus is helpful in delimiting the fertile days. ¹⁴ Insemination is useless if the canal is exuding thick, viscid, opaque-looking mucus.

There is controversy in the literature regarding the value of coitus a few hours preceding artificial insemination in order to produce orgasm and thus perhaps increase the likelihood for ovulation. I have never suggested this to my patients and therefore know that preliminary coitus is not essential to success, and I doubt very much that it either favors or retards it.

All artificial inseminations are performed in my office, not in the hospital. I place the patient in the lithotomy position and elevate the hips slightly by cranking up the middle of the office table. A non-sterile, unlubricated, bivalve speculum is inserted and the external os exposed. The blades of the speculum are relaxed so that the cervix just lies free between them. The semen is aspirated in a dry non-sterile 5 cc. glass syringe to which a metal, intravenous cannula is attached. Without either wiping away or displacing the mucus from the cervical canal, the point of the cannula is introduced 0.5 to 1 cm. within the external os and the semen spurted into the canal in four or five thrusts of the plunger of the syringe, simulating the mechanism in normal ejaculation. As the speculum is withdrawn, the blade is wiped back and forth across the external os half a dozen times to bathe it in the seminal pool which has been formed by the semen running out of the cervix. A piece of absorbent cotton is placed superficially in the introitus to prevent soiling of the clothes with the semen. The end of the table is elevated, and the patient remains on her back with the legs extended in a comfortable position for 20 minutes, the hips still raised. She then gets up and goes about the day's routine. The patient should not have uterine cramps, and if she does it means that the cannula was inserted too high within the canal and some semen got into the uterus. After all, semen with its pungent hyperalkalinity acts distinctly as an irritating foreign body in the human uterus. Certainly, following coitus, the spermatozoa normally swim out of the semen deposited in the lower cervical canal and, by the time they gain access to the uterus, have been washed free of the seminal plasma by friendly cervical mucus.

Using this technique on thirty-six apparently-fertile women, I have

obtained twenty pregnancies. Five women are still being treated. The latter have had a total of fifty-four inseminations, with no success as yet. Eleven patients have discontinued treatment after from one to fourteen inseminations; the total for the group being sixty-four treatments. Four women in the successful group had a single insemination the month of impregnation, twelve had two treatments that month, three patients had three and one woman had four. The number of months required for success varied. Five patients became pregnant immediately the first month, eight the second month, two the third month, one the fourth month, three the fifth month and one after 23 months. It is noteworthy that thirteen of the twenty successful results occurred after only one or two months treatment, which usually involved a total of two or four inseminations. This means that if heterologous artificial insemination is likely to succeed, it will succeed very quickly, and if it does not succeed within the first 2 months, the prognosis is much less favorable. Of course this does not mean that long persistence of treatment is useless; it simply means that if it does not succeed within the first 2 months the ultimate prognosis remains in doubt. There is no reason to believe that the fertilizing index of artificial insemination is very different from that of ordinary coitus. Probably the majority of couples attain pregnancy after 2 months of coitus without contraceptives and those who do not, scatter along the wayside at the various monthly milestones. The only advantage of artificial insemination is that we are always dealing with males of known sperm normality.

If after 3 months of effort, heterologous insemination does not succeed, the woman should have a careful sterility investigation. I do not do this earlier because in a fair proportion of cases it is unnecessary since pregnancy occurs so promptly. The patient who required 23 months for success was my first patient, on whom, from a lack of knowledge, I was performing intrauterine insemination. Omitting this first case, the other nineteen successful cases required a total of ninety-four inseminations, or an average of five per case. The equal effectiveness of artificial insemination and normal coitus is suggested by the following case:

A woman aged 31 whose husband, a teacher, was her first cousin, had had two pregnancies, each occurring the first month in which contraceptives were abandoned. The first pregnancy resulted in an acraniac fetus and the second in a spontaneous abortion showing defec-

tive germ plasm. In order to dilute the abnormal genes which were so tragically aligned through consanguinity, they requested artificial insemination. This was done on the fourteenth and seventeenth days of her cycle, which varied from 28 to 35 days. Despite a moderate cervical erosion, she became pregnant the very first month, exactly as she had done previously after coitus. Unfortunately, shaking up the genes did not help, for this time she had a missed abortion when 6 months pregnant.

While doing intravaginal inseminations and inseminations into the lower part of the cervical canal, I have never stirred up or caused a single case of endocervicitis or salpingitis. If the donor is free of venereal disease, inseminations that do not invade the uterus are free of danger. In the one case in which I did intrauterine inseminations, my first case, a very mild, low grade inflammation of the right tube developed about 48 hours after a treatment. It subsided rapidly and has never recurred.

Among our successful inseminations there have been a number of pathologic results, more likely due to a sampling error than to the way conception occurred. Among sixteen pregnancies which have terminated there was one premature separation, one placenta previa, one ectopic pregnancy, one early abortion and two missed abortions, yielding a total of eleven healthy living children. Four patients remain undelivered.

As stated earlier, I have had little or no experience with intrauterine insemination. If used, it should be reserved for cases in which the husband's semen is injected, to compensate in some doubtful way for its inherent defects or to impregnate a wife who is refractory to ordinary impregnation for some mechanical reason. My skepticism of the value of artificial insemination in the treatment of ordinary sterility is overwhelming and it is difficult for me to keep an open mind.

Schultze^s goes into lengthy Teutonic detail about the technique of intrauterine insemination, and I shall condense his material. He insists that the inseminations be performed in a hospital. The donor, in an adjacent room, is provided with a dry sterile beaker wrapped in a sterile towel. He is also provided with a bell to announce the successful completion of his part in the procedure. While the specimen is being obtained, the recipient is placed in the lithotomy position, and the vulva, vagina and cervix are prepared as for a vaginal operation. A warm dry speculum exposes the cervix. As soon as the semen is collected it is

aspirated into a warm sterile syringe which is attached to a small catheter that has been inserted into the fundus. Schultze then clamps the cervix to prevent a reflux of the semen into the vagina and slowly injects the whole ejaculate (from 1 to 3 cc.) under very little pressure. He then washes out the catheter by following the semen with 1 to 2 cc. of warm sterile dextrose. A little of the semen often gets into the tubes and sometimes even into the peritoneal cavity. The catheter is then clamped off and strapped to the patient's thigh. It is left in position for two hours and removed. The patient is kept in the hospital overnight. If uterine cramps are severe enough to disturb the stoical German Hausfrau, a mild sedative is administered.

Schultze warns of the danger of infection, which he claims is glossed over in many reports. Franz has reported a case of fatal sepsis following the intrauterine technique.

Schultze states that many authors prefer to inject only one or two drops of semen into the uterus; however, most German authorities prefer to use the whole amount.

THE SELECTION OF A DONOR

Elaborate criteria have been evolved to apply to the selection of a donor. Weisman in a recent article lists fourteen points to be considered in each case.15 He stresses the importance of superior mental and physical health, a desirable family lineage, fertility proved through previous procreation, age between 30 and 35, excellence of character and willingness to cooperate indefinitely in the experiment. The physical characteristics and racial stock of the donor must coincide with the husband's. Weisman recommends that the emotional make-up of the donor and the husband should be carefully studied by the physician through several meetings with each so that they may be perfectly matched. The religion should be similar or as close to the husband's and wife's as possible. Weisman nominates "physicians and true scientists" as ideal donors. He seriously objects to young unmarried medical students and interns as a source for semen, an objection I do not share. He prefers that the donor and husband should have the same blood group, and recommends when feasible that multiple semen specimens should be used in the same patient; then, even the physician can never know whose spermatozoa sired the infant.

In the abstract I agree with much of this, but in actual practice, at

least in provincial Baltimore, it is impossible to follow the whole program. Perhaps our ceiling is too low (we pay a maximum of \$5.00 for each specimen), or we have too few "true scientists," at least too few with the proper attitude. At all events we can not be nearly as selective as Dr. Weisman, for specimens are too difficult to obtain. Furthermore, on a philosophic basis I question whether such exact care in selection is desirable. It is debatable whether breeding supermen is wholely desirable, perhaps high mediocrity is a safer and wiser goal.

I choose my donors from the married and unmarried medical students and house officers. I question them about venereal disease and undesirable hereditary traits. Their intelligence is guaranteed by their academic advancement. I note their size, coloring, religious origin and racial stock, and from a group of five choose the one who most closely approximates the husband in these several particulars. The fertility is established by semen study and eventually by having previously been successful donors. The men are of such a type that I truthfully feel the child to be conceived is fortunate to have so superior a father.

MORAL AND LEGAL PROBLEMS

If the husband is the semen donor, no moral or legal difficulty presents; but when the semen is secured from another source many special situations arise. However, I think they are not as dangerous and formidable as many of my colleagues or the editorial board of the Journal of the American Medical Association consider them. 1,12,15,16,17 Perhaps I am unusually trusting, or provincial medicine is a more forthright and uncomplicated art than that met in the great metropolises of New York and Chicago. I believe that if a doctor is honest and uses his God-given common sense no serious problem exists in a heterologous insemination.

Some months ago I summarized my own practice in the following credo:

Rule one: The donor must remain completely anonymous to the recipient and the husband, and the recipient and the husband must remain equally anonymous to the donor.

Rule two: Before attempting artificial insemination, know the couple: their intellectual capacity and emotional stability, and if possible the likelihood of a permanent marriage. Only a small percentage of patients applying qualify for so radical a social procedure. When a doctor con-

sents to do an artificial insemination from an unrelated donor, it is really the couple's insignia of good character. Artificial insemination must always be completely individualized. It should never be an assembly-line kind of medical treatment.

Rule three: Never urge the procedure; if either husband or wife are lukewarm, drop it completely.

Rule four: Forget signed papers. If the patients are carefully selected, contracts and agreements are unnecessary, and simply act as a permanent reminder of something which should be forgotten as quickly and completely as possible. In the ideal case, by the time the patient reaches term, the woman, the husband and the doctor have to think twice to remember that the pregnancy is physically not the husband's, for psychically it has become his.

Rule five: Accord paternity to the husband both in the hospital record and the birth certificate. Here a white-lie is a kindly, humane act.

Rule six: Make the fees low; keep artificial insemination out of the mercenary column. View it as a personal medical service, the contribution of an aesculapiad to the happiness of some wretched, worthy, sterile couple.

Many of you may hold serious objection to rule four, since if legal proceedings are entered into at any time after the child's birth it may be declared a bastard, unless signed permission had been registered by the husband. There is even some doubt that the husband's signed permission would necessarily invalidate this possibility, but thus far the matter has not been put to a legal test. Then too, if the child is the husband's beneficiary, its share of an estate may be contested unless it had been legally adopted by the husband. I recognize these possibilities, but if one is going to submit a child, conceived by artificial insemination, to all this glaring publicity, it robs the procedure of the one big advantage it possesses over adoption. Artificial insemination is supposed to make the world believe, and therefore the couple feel, that the infant is theirs, theirs just as much as if it was conceived upon the marriage bed. Therefore, with naive faith in my fellow men I omit all legal proceeding and telltale signatures.

In regard to the fifth rule. It is a violation of the law to falsify the birth certificate. But of what earthly medical, statistical significance could it be that Jimmy Jones and not Sammy Brown sired Sammy Brown, Jr. It is a violation like burning leaves in the street so they will

not scatter over the neighbor's lawn. It is the type of offense in which the good accomplished, completely neutralizes the infraction of a law.

Following this unorthodox credo, a successful artificial insemination has become one of the most satisfying of all medical experiences. It would require a petrified heart not to warm to the scene of a sterile father doting on his two children, who, according to the neighbors, resemble him very closely.

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PROCEEDINGS OF ACADEMY MEETINGS

STATEDMEETINGS

March 4-The New York Academy of Medicine. Executive session-Reading of the minutes. ¶ Papers of the evening, Plasma Proteins and Amino Acids-a] Plasma proteins, amino acids and parenteral feeding, Sidney C. Madden, Assistant Professor of Pathology, University of Rochester, School of Medicine and Dentistry; b] Serum proteins in relation to liver disorders, Joseph Post, 1st Lt., Medical Corps, A.U.S., Ashford General Hospital, White Sulphur Springs, West Virginia; Arthur J. Patek, Jr., Associate in Medicine, College of Physicians and Surgeons, Columbia University. TReport on election of

March 18-The Harvey Society in affiliation with The New York Academy of Medicine. The Sixth Harvey Lecture, "The Absorption of Vitamin A and Its Storage in the Tissues," Samuel W. Clausen, Professor of Pediatrics, University of Rochester School of Medicine.

Fellows.

SECTION MEETINGS

March 2-Dermatology and Syphilology. ¶ Presentation of cases—a] From the New York Polyclinic Hospital; b) From the City Hospital; c] Miscellaneous cases. ¶ Discussion. ¶ Executive session -a] Reading of the minutes; b] Appointment of Nominating Committee.

March 5-Surgery. [Executive session-a] Reading of the minutes; b] Appointment of Nominating Committee. & Case presentations—a] One-stage resection of carcinoma of the head of the pancreas with implantation of the pancreatic stump into the jejunum. Fourteenmonths' follow-up, Charles G. Child, III (by invitation); b] Adenocarcinoma of the terminal portion of the common bile duct. One-stage modified Whipple operation, Ralph Colp; d] Two-stage resection of carcinoma of the head of the pancreas with metabolic studies. Twoyear follow-up, George T. Pack, Paul Rekers (by invitation), Cornelius P. Rhoads. | Papers of the evening-al One-stage resection of carcinoma of the head of the pancreas, Charles G. Child, III (by invitation); b] Observations on effects of experimental exclusion of the external pancreatic secretion, Benjamin N. Berg. ¶ General discussion, Allen O. Whipple.

March 9-Combined Meeting Neurology and Psychiatry and the New York Neurological Society. ¶ Case presentations-Electrotherapy in the treatment of vocal cord paralysis and facial spasm, Charles O. Fiertz (by invitation). ¶ Papers of the evening-a] Psychic determinism in Holmes and Freud, Clarence P. Oberndorf, Discussion-Leland E. Hinsie, Phyllis Greenacre, Iago Galdston; b] A theory concerning the neural mechanism of stuttering, Samuel T. Orton. Discussion-I. S. Wechsler, Stanley Cobb (by invitation); c] Use of electroencephalography in the War effort, Bernard L. Pacella (by invitation). Discussion-S. Eugene Barrera (by invitation), Major Benj: min H. Balser (by invitation). ¶ Executive session of the Section. Appointment of Nominating Committee.

March 10-Historical and Cultural Medicine. ¶ Executive session-a | Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee ¶ Paper of the evening, Copernicus Celebration, Honoring the Quadricentenary of the publication of De revolutionibus orbium caelestium, Nicholas Copernicus and the Birth of Modern Science (1543-1943), Edward Rosen, Ph.D., Department of History, College of the City of New York (by invitation). Discussion-William Stahl, Ph.D., Department of Classics, New York University (by invitation). ¶ Exhibition of books by and on Nicholas Copernicus.

MARCH 11—Pediatrics, Residents' Meeting.

[Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. [Papers of the evening—a] From Long Island College Hos-

pital, Major nephropathies in forty children with pyuria, Elizabeth J. Ittner (by invitation); b] From New York Hospital, Subdural hematoma in the neonatal period, Thomas F. Henley (by invitation). Discussion-Samuel Z. Levine; c] From Babies Hospital, Staphylococcus aureus empyema, Conrad M. Riley (by invitation). Discussion-Rustin McIntosh; d] From New York Post-Graduate Medical School and Hospital. A group of cases of severe infantile eczema, Paul di. Sant' Agnese (by invitation). Discussion-Vincent de Paul Larkin (by invitation); e] From Bellevue Hospital, Department of Pediatrics. An evaluation of the esophogram in children, Eleanor Galenson (by invitation), Bernard E. LeVine (by invitation). Discussion-Harry Bakwin.

March 15-Joint Meeting of Ophthalmology with the New York Society for Clinical ¶ Instruction Ophthalmology. Pharmacology as applied to the internal muscles of the eye, Ervin Tusak. \ View of exhibits of Pharmaceuticals used in Ophthalmology. ¶ Executive session of the Section-al Reading of the minutes; b] Appointment of Nominating Committee. Paper of the evening, The present status of tuberculin therapy from the internist's point of view, Edgar Mayer. Discussion.-I. Rappaport, Alan H. Woods (by invitation). I Sym-Table Discussion, posium - Round "Non-surgical therapy in ophthalmology," Francis H. Adler, Philadelphia (by invitation), Sanford R. Gifford, Chicago (by invitation), Mark Schoenberg, Alan H. Woods, Baltimore (by invitation).

March 16—Medicine. Treading of the minutes. Trapers of the evening—a] Psychosomatic considerations of arterial hypertension, Carl Binger. Discussion—Asa L. Lincoln, George Daniels; h] Psychosomatic aspects of gastric function, Harold G. Wolff. Trapers discussion. Texecutive session, appointment of Nominating Committee.

MARCH 17—Otolaryngology. ¶ Reading of the minutes. ¶ Case reports, A case of otitic encephalitis, Clarence Smith. Discussion—Lester Hubby, James Louis Joughlin. ¶ Paper of the evening, The eustachian tube, Dorothy Wolfe (by invitation). Discussion—Wendell Krieg (by invitation), Edmund Prince Fowler. ¶ General discussion. ¶ Executive session, appointment of Nominating Committee.

MARCH 19—Orthopedic Surgery. ¶ Reading
of the minutes. ¶ Papers of the evening—a] The modern concept of diagnosis and treatment of weak feet,
Armitage Whitman (by invitation); b]
The role of gravity in foot disorders and deformities, Dudley Morton (by invitation); c] Evaluation of foot function by measurement, R. Plato Schwartz (by invitation). Discussion—Arthur Krida, John J. Nutt. ¶ General discussion. ¶ Executive session, appointment of Nominating Committee.

23-Obstetrics and Gynecology. March ¶ Executive session-Reading of the minutes, appointment of Nominating Committee. ¶ Case reports-Chondrodystrophy-report of a case and review of the literature, Joseph N. Nathanson (by invitation). ¶ Papers of the evening—al (In Commemoration of the Oliver Wendell Holmes Centennial) History of puerperal infection in America during the last century, Claude Heaton; bl Chronic glomerulonephritis with a nephrotic syndrome complicated by pregnancy, Joseph E. Corr. Discussion by Richard Johnson, Associate Professor of Medicine, Wayne University, Detroit, Michigan. ¶ General discussion.

March 25—Combined Meeting. Genito-Urinary Surgery in conjunction with New York Urological Society at the Yale Club. Paper of the evening— Intrinsic and extrinsic uretero-pelvic obstruction as an entity and its treatment, Clyde Leroy Deming, New Haven, Conn. Executive session of section, appointment of Nominating Committee.

AFFILIATED SOCIETIES

March 15-New York Roentgen Society in

affiliation with The New York Academy of Medicine. Papers of the evening—a] The roentgen study of atypical (virus?) pneumonia—(1) Parrot and pigeon psittacosis, Ross Golden; (2) Pathology of atypical pneumonia, Edith Sproul (by invitation); (3) Roentgen studies of atypical pneumonia, Philip Brown (by invitation; b] Mass roentgen survey of the stomach—Fordyce B. St. John (by invitation), Harold D. Harvey (by invitation), Paul S. Swenson, Executive session.

MARCH 17-New York Section of the Society for Experimental Biology and Medicine. [Papers of the evening-a] The influence of filtrate factor deficiency, cortin, or desoxycorticosterone acetate on survival of adrenalectomized rats, Elaine P. Ralli; b] Fatal loss of plasma volume after lymph heart destruction in toads, R. L. Zwemer, V. G. Foglia (by invitation); c1 The influence of the body temperature and the application of heat on the blood pressure of rats, Irving Graef, George G. Proskauer (by invitation), Charles Neumann (by invitation); d] Studies on the titration and neutralization of the western strain of equine encephalomyelitis virus in tissue culture, C. H. Huang (introduced by Murray Sanders); e] Lung tumors following intraperitoneal injection of 1:-2:5:6-dibenzanthracene into young mice of three strains, Clara J. Lynch; fl The presence in various grains of factors inhibiting tumor growth, R. Lewisohn, D. Laszlo (by invitation), C. Leuchtenberger (by invitation), R. Leuchtenberger (by invitation), Z. Dische (by invitation); gl Treatment of spontaneous breast cancers in mice with pearled barley, R. Lewisohn, C. Leuchtenberger (by invitation), R. Leuchtenberger (by invitation), D. Laszlo (by invitation), Z. Dische (by invitation).

March 25—New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Paper of the evening—Malignant lymphoma: a clinicopathologic survey, Tracy B. Mallory, Boston (by invitation). ¶ Executive session.

CATHS OF FELLOWS FOR STATES OF STATE

Brown, David Chester, Danbury Connecticut; born in Norfolk, Virginia, November 16, 1863; died in Danbury, Connecticut, May 12, 1943: graduated in medicine from the Yale University School of Medicine in 1884; elected a Fellow of the Academy March 7, 1907. He was surgeon to the Danbury Hospital, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

EWING, JAMES, 444 East 68th Street, New York City; born in Pittsburgh, Pennsylvania, December 25, 1866; died in New York City, May 16, 1943; graduated in medicine from the College of Physicians and Surgeons, New York City in 1891; elected a Fellow of the Academy, June 3, 1897; a member of the Committee on Public Health Relations in 1913 and 1914 and a member of the Committee on Medical Education in 1924 and 1925, and in 1932 and 1933. Dr. Ewing was a member of the State and County Medical Societies, he was qualified under the Workmen's Compensation Law of New York State as a specialist in pathology, a member of the Association of American Physicians, of the American Society of Pathologists and Bacteriologists, of the American Society for Cancer Research, the New York Pathological Society, and Consulting Pathologist to the Memorial and New York Hospitals. He was one of the world's leading authorities on cancer and was a former director of the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

HALL, JOHN MEAD, 568 Park Avenue, New York City; born in Norwich, New York, October 13, 1880; died in New York City, June 7, 1943; graduated in medicine from Cornell University Medical College in 1901; elected a Fellow of the Academy, February 7, 1918. Dr. Hall was a member of the State and County Medical Societies, a member of the New York Otolaryngological Society, and a member of the Society of Alumni of Bellevue Hospital. He was senior assistant surgeon in otology at the New York Eye and Ear Infirmary.

MAYER, MAX DAVID, 1192 Park Avenue, New York City; born in New York City, February 23, 1893; died in New York City, May 28, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1915; elected a Fellow of the Academy March 2, 1933. Dr. Mayer was a diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the State and County Medical Societies. He was associate gynecologist to the Mount Sinai Hospital, and attending gynecologist and obstetrician to the Sydenham Hospital.

New York City; born in Alexandria, Pennsylvania, March 27, 1862; died in New York City, May 6, 1943; graduated in medicine from University and Bellevue Medical College in 1886; elected a Fellow of the Academy April 19, 1928. He was a former director of the medical division of Harlem Hospital, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

PARRY, ELEANOR, Huntington, Long Island, New York; born in Rome, New York, November 22, 1860; died in New York City, May 22, 1943; graduated in medicine from the Woman's Medical College of the New York Infirmary for Women and Children in 1894; elected a Fellow of the Academy February 4, 1909. Dr. Parry was former resident physician of Mount Holyoke College, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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1943

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BULLETIN OF

THE NEW YORK ACADEMY OF MEDICINE



SEPTEMBER, 1943

MALARIA AND ITS INFLUENCE ON WORLD HEALTH

The Hermann M. Biggs Memorial Lecture*

PAUL F. RUSSELL

Lt. Colonel, Medical Corps, Army of the United States, Chief, Tropical Disease and Malaria Control Section, Preventive Medicine Division, Office of The Surgeon General, U. S. Army

Introduction

the most important of all diseases in the world today."
This statement is based on wide experience and great authority, for it is the first sentence in that excellent treatise on tropical diseases by Admiral Stitt and Colonel Strong. Adequate morbidity and mortality statistics regarding malaria do not exist, yet it is generally believed by those who have studied the subject, that no disease has, or has had through centuries, a more profound influence on world health than malaria. Medically oriented historians suggest that this disease has postponed development of the tropics for centuries, and that it has accelerated the decline of nations. Even today this preventable mosquito-borne infection is the greatest enemy of merchant, soldier, administrator, and farmer in all of the warmer countries.

[.] Given April 1, 1943 at the Stated Meeting of The New York Academy of Medicine.

Such sweeping assertions seem rash in the United States where in 1941 the mortality rate for malaria in fourteen Southern states was only 2.73 per 100,000.² Taking the census registration area of the whole country, the death rate from malaria in 1900 was 7.9 per 100,000 but only 1.1 in 1940.³ Relatively few can recall local conditions of six or seven decades ago when our South was highly malarious and even such northern states as Michigan, Illinois, Indiana, and Ohio were afflicted. For instance, the death rate from malaria in Michigan in 1880 was 19.5 per 100,000. As late as 1900, Memphis had a malaria mortality rate of 200 per 100,000, and Savannah almost as great.⁴ High as these urban malaria rates appear, they were about a fifth of those obtaining in such tropical cities as Singapore as late as 1911.⁵

Malaria at present extends as far north as 60° N. latitude (in Russia) and as far south as 40° S. latitude (in Argentina). It is found as low as the Dead Sea (1,300 feet below sea level) and as high as Quito in Ecuador (9,000 feet). But malaria is a focal disease and is not evenly distributed nor uniformly prevalent in any country. In the United States it is most common in the southeast, although it extends as far north as Illinois and Indiana, and also occurs in California.

There is a great deal of hyperendemic malaria between 45° N. and 40° S. latitude, in the plains and foothills of Central America, north and northeast South America, Central Africa from the Atlantic to the Indian Ocean, North Africa, south and especially southeast Europe, Turkey, the Levant, Iraq and Iran, Afghanistan, India, Ceylon, Burma, South China, Indo-China, Siam, Malaya, Netherlands Indies, Formosa, the Philippines, and many islands of the Pacific which are west of 170° E. longitude and north of 20° S. latitude. (The Fiji Islands and Samoa, for example, are not malarious but the New Hebrides suffer severely.)

Malaria is hyperendemic in many areas of the littoral of some of the world's great seas and gulfs, the names of which connote vistas of sand and coral, mangrove and coconut, with a wide variety of peoples and topography, encircling the globe. The Caribbean, Mediterranean, Tyrrhenian, Ionian, Adriatic, Aegean, Black, Azov, Caspian, Red, Arabian, East and South China, Sulu, Celebes, Java, Banda, Timor, Arafura, and Coral seas, the Bay of Bengal, the gulfs of California, Mexico, Honduras, Panama, Guinea, Persia, Oman, Siam, and Tonkin, all are bordered, in part at least, by highly malarious regions.

To many of the countries within the hyperendemic malaria zones this disease, which has been a medical curiosity in much of our own country, is bringing not only physical disaster but economic and social tragedy. In India, for example, malaria is a veritable juggernaut disease. There it kills at least a million persons every normal year, more in epidemic times. Another million die from indirect results of malaria. Throughout all Hindustan there are each year at least 100,000,000 cases of malarial fevers. Quoting Sinton: "There is no aspect of life in that country which is not affected, either directly or indirectly, by this disease. It constitutes one of the most important causes of economic misfortune, engendering poverty, diminishing the quantity and the quality of the food supply, lowering the physical and intellectual standard of the nation, and hampering increased prosperity and economic progress in every way."

Hehir, a competent observer, wrote: "It may with confidence be said that the eradication of malaria in India would in a single generation convert that country into one of the most prosperous in the world." It is now one of the least prosperous so far as the vast majority are concerned. Average incomes in rural South India are as low as a dollar a month.

What the actual sum total of malaria is today, no one knows, or can estimate closely. But one would venture to assume from such data as are available and from personal acquaintance with certain areas, that there are not less than 3,000,000 malaria deaths and at least 300,000,000 cases of malarial fevers each year, throughout the world.

These facts are of greater concern to us now than ever before. In this global war our armed forces are operating in some of the world's most malarious areas. We have already felt the impact of this debilitating fever in such places as Panama, West Africa, Burma, New Guinca, and the Solomon Islands. In such areas malaria is by all odds the greatest disease hazard to our soldiers; indeed, in some places it is a greater menace than the enemy. To more than one of our medical officers malaria is no longer an exotic disease but a difficult military problem.

EARLIEST DAYS

The history of malaria extends so far back into antiquity that speculations as to when and where it first appeared are futile. Certainly the

present great library of malariology represents cumulative endeavors of many generations of priests and philosophers, parasitologists and physicians.

In early days, when natural causes of all disease were hidden, it was inevitable that man should attribute malaria to black magic of wizards, evil eyes of enemies, offended spirits of dead men, animals, or plants, maleficent mediation of gods and goddesses of wood and stone. Malaria prophylaxis was then, as it is in Central Africa and the Solomon Islands today, a practice of white magic, charms and spells, fetishes and taboos, plant lore, and sacerdotal hygiene, a hocus-pocus conjured up to exorcise, conciliate, or propitiate superhuman beings and powers.

Gradually man came to prefer natural to supernatural explanations. Still looking through a glass darkly, he spoke of malaria epidemics as dependent on alterations in astral currents or lunar rays, or generated by terrestrial perturbations and tremors. He discoursed learnedly of febrific effluvia, vegeto-animal exhalations, and mephitic airs.

ANCIENT GREECE AND ROME

The ancient Greeks 2,000 years ago recognized quartan, tertian, quotidian and semitertian (probably malignant tertian) varieties of malaria. They also were aware that the disease had seasonal and topographical features. In particular, they associated the intermittent fevers with marshes and marsh vapors. Hippocrates in the fifth century B.C., wrote of the enlarged spleen of inhabitants of marshy regions.

Then there was a Greek story (perhaps apocryphal) of Empedocles of Agrigentum who controlled an epidemic in Selinus, Sicily, about 550 B.C., partly by draining the marshes and partly by turning two rivers into them so that, as Matthew Arnold wrote, Empedocles was able to "cleanse to sweet airs the breath of poisonous streams." Whether or not Empedocles was dealing with malaria, certainly there are many passages in the Greek which clearly connect this fever with marshes.

Roman writers, also, were acquainted with paludism and were suspicious of swamps. For instance, the Republican agriculturalist, Varro (116-28 B.C.), in his Rerum Rusticarum wrote that in marshes "certain minute animals are bred, invisible to the eye and, borne by the air, reach the inside of the body by way of the mouth and nose, and cause diseases which are difficult to be rid of." 10

Fabius Maximus and Julius Caesar suffered from intermittent fever

and during the Civil Wars the health of Caesar's army was shattered by it. 10 Cicero wrote of the "old Fever Temple on the Palatine," indicating that the cult of the Fever Goddess in Rome was very ancient.

Then, too, there was a famous passage from Columella (about the first century B.C.) which stated that "marshes threw up noxious steams and bred insects, armed with mischievous stings, and pestilent swimming and creeping things whereby hidden diseases were often contracted, the causes of which even the physicians themselves could not thoroughly understand."¹⁰

Thus, in ancient Italy, as in ancient Greece, both medical and lay authors recognized the intermittent fevers and clearly surmised an etiological relationship between these fevers and low marshy places. This is easy to understand because the malarial fevers, with their characteristic periodicity, even to this day in Greece and in Italy are often most prevalent near marshes. There was a good deal of malaria in ancient Greece, where it was apparently introduced during the fifth century B.C. In fact, Ross, Jones, and others have suggested that malaria was a contributing factor in the great decline in moral and intellectual vigor which took place in Greece between 500 and 300 B.C. It has also been postulated that malaria had a similar disintegrating effect in ancient southern Italy. Some historians, as Childs, believe that while disease is mighty over the individual, parasites and viruses have played an unimportant role in social history.

However that may be, by the latter part of the Middle Ages, the "Roman Airs" had a bad name throughout all Christendom. For instance, Celli¹⁰ records that Peter Damian in the eleventh century tried to give up the episcopal see of Ostia, forced on him by Pope Stephen IX. He wrote the following verses:

"Rome, voracious of men, breaks down the strongest human nature, Rome, hotbed of fevers, is an ample giver of the fruits of death."

In the twelfth century, Roman fevers are said to have destroyed the army of Frederick Barbarossa, and this was commemorated in verse by Godfrey of Viterbo, who wrote

"Those from whom Rome was unable to defend herself, were dispersed by the air

at whose breath the German youth fell."

The great Arab physicians of the eighth to thirteenth centuries wrote of these intermittent fevers but, in general, active interest and

speculations on etiology subsided with Galen in 200 A.D., not to be aroused again until the seventeenth century.

SEVENTEENTH AND EIGHTEENTH CENTURIES

In the seventeenth and eighteenth centuries there were great advances in knowledge of therapy and of etiology of intermittent fevers.

THERAPY

In the seventeenth century European physicians learned that the bark of a South American tree is an effective remedy for the intermittent fevers. There have been many accounts as to how this came about. Apparently the bark was first known in Peru, where the first recognized use of this bark was in 1630,18 but whether natives had recognized its medicinal qualities before Pizarro invaded their country in 1512-1533 is unknown. The traditional anecdote, dating back many years, appears to have little historical basis. It told of the fever of Ana de Osorio, the first, or of Francisca Henriquez de Ribera, the second wife of the fourth Count of Chinchon, Viceroy of Peru. A friend, as the story goes, sent to the Count's physician a parcel of powdered bark of the quina-quina tree, a substance that had once cured him of "tertiana." The physician, Don Juan de Vega, having tested the powder on a number of patients, is reported to have administered it to the Countess with great success. About 1640, the enthusiastic Vicereine, or her physician, or some Jesuit father, is said to have sent or carried samples to Europe.

This story has suffered a serious blow in the recent discovery of the official diary of the Count of Chinchon, ¹⁴ wherein is a careful day-by-day account of the Chinchon family. It now appears that the first countess was blessed with amazing good health. Aside from a sore throat and a "flux and cough on the lungs" she had no illness at all in Peru. The noble count himself was frequently ill with malaria, but nowhere is it recorded that he experienced a dramatic cure by fever bark. The countess did not take bark back to Europe, for she died in Colombia, on the way home, of what seems to have been yellow fever.

The true, albeit less romantic, account of the advent of cinchona bark in Europe appears to be that of Haggis, 15 who made a scholarly search among original documents. He notes that during the last decades of the sixteenth and throughout the seventeenth century there was a

brisk trade in medicinal barks and herbs from South America to Spain and Italy. One item in considerable demand was a bark, which because of its medicinal properties was called quinua-quinua by Peruvians and which is now known to have been from the tree Myroxylon peruiferum. In commerce this bark was referred to sometimes as Peruvian and at other times as quina-quina bark. Peruvian balsam was extracted from it and was used as a non-specific febrifuge. When demand came to exceed supply, the exporters began to substitute another bark of similar appearance, which from the evidence must have been taken from cinchona trees. For some decades during the seventeenth century the dual source of so-called Peruvian bark led to confusion among physicians as to its real value in treating the intermittent fevers. But gradually the adulterant replaced the original bark completely. Thus, as has been pointed out,14 it would appear that we owe the discovery of one of our most useful chemotherapeutic remedies to dishonest traders rather than to keen-eyed scientists.

The earliest mention in European literature of the use of cinchona was by Heyden in 1643, so the remedy must have been introduced before that. Powdered bark had been sent from Spain and Italy to England by 1655 and was used in this form against the intermittents for about two centuries. The bark was known in the North American colonies. For instance, in 1776 the Continental Congress ordered the medical committee to forward 300 pounds of bark to the southern department for use of the troops. Jackson, a British Army surgeon in the forces of Lord Cornwallis, used the bark extensively to treat intermittent fevers among British troops in their southern campaigns. 16

The first man to describe the fever tree scientifically was Charles Marie de la Condamine, an astronomer, who in 1735 led an expedition from France to measure an arc of the meridian near Quito, Ecuador, in order to determine the shape of the earth. He quarreled with his associates and quit them to explore the Amazon, and eventually the Peruvian country. But it was the Swedish botanist, Carl von Linne, the great Linnaeus, who gave the name Cinchona to the quina-quina tree. His misspelling of the name of the Countess has been perpetuated.

Two French pharmacists, Pelletier and Caventou, isolated the alkaloids quinine and cinchonine from cinchona bark in 1820. Since then many other alkaloids have been isolated from this Peruvian bark but only four occur in any considerable amounts. These are quinine and

quinidine, cinchonine and cinchonidine, all of which exert a therapeutic action on malaria.

Demand for cinchona bark increased rapidly, and the trees, which grew wild, were recklessly destroyed. It occurred to several scientists that the tree could probably be grown in other tropics as well as South American. In 1743, de la Condamine attempted to take cinchona plants to Europe but they were all swept off his ship by a wave in the river Amazon before he had even left South America. In 1849, cinchona trees were planted unsuccessfully in Algeria. The Dutch, in 1852, sent Justus Charles Hasskarl, a courageous botanist, on a hazardous collecting expedition which took him across the Andes into Bolivia and Peru. He was successful, by a narrow margin, and began cinchona cultivation in Java in 1854. His Government rewarded him with a knighthood of the Netherlands Lion and a Commandership of the Oaken Crown.

In 1860, the British sent out a party under the exceptionally able leadership of Clements R. Markham, a geographer and archaeologist. As a result of his work a cinchona plantation was started in the Nilgiris Hills of Madras Presidency near Ootacamund, where over two and a half million trees were growing by 1872. This plantation is still a source of government quinine for use in India. Markham was knighted for his achievements.

The seeds and seedlings of these early Dutch and British expeditions were not the best yielding varieties of the fifty or more species of cinchona trees growing in South America. The most successful collector of high quality seeds was an Englishman named Charles Ledger who had been living in the cinchona belt and knew the difference between strong bark and feeble. He sent his West Indian servant Manuel for seeds of a tree which he knew had a high quinine content in its bark and which he had seen growing in a certain place. The good Manuel was gone five years, because four April frosts destroyed the flowers and prevented ripening of fruit of the particular trees which met his requirements. But, finally, he came back with the seeds. Sent out again he was seized by Bolivian officials, jealous of their bark monopoly, and, although imprisoned, severely beaten, half-starved, and robbed of all his possessions, he refused to tell for whom he was collecting seeds and was at last set at liberty, to die soon afterwards of his ill-treatment.

Ledger, in 1865, sent fourteen pounds of high quality seeds to his

brother George, who lived in London. George Ledger attempted to sell them to the British Government who were not interested. However, he finally sold half of the seeds to the Dutch for a few guilders and the other half to a Madras planter. Within eighteen months of this sale the Dutch had 12,000 plants ready to set out and five years later their analyses of bark were showing from 8 to 13 per cent of quinine, whereas no other bark on the market could show much over 4 per cent. The seeds sent to Madras also in time grew well but on a much more limited scale; this species was officially named Cinchona ledgeriana. The Dutch did a good deal of experimenting with hybrids and successfully developed the world's best cinchona trees. At the outbreak of this war, Java had some 37,500 acres of cinchona, producing more than 20,000,000 pounds of bark a year—what amounted to probably the most effective crop monopoly of any kind in all history.

Quinine, the alkaloid, was prepared commercially in Philadelphia in the United States as early as 1823¹³ and has been prescribed therapeutically in this country ever since. The use of prophylactic quinine was advocated in this country as early as 1844¹⁷ and was employed successfully among negro slaves during the construction of the Charleston and Savannah Railway.¹⁵

The introduction of cinchona bark into Europe enabled Morton in England in 1697 and Francesco Torti in Italy in 1712 to suggest that the paludic fevers could be separated from all others, not only by the typical periodicity (which was not evident in all cases) but also by their favorable response to cinchona bark treatment.9

Today the Japanese control all the cinchona of the Netherlands Indies and, with their Axis partner, Germany, they also control the Dutch stocks of cinchona alkaloids, together with the quinine factories. Consequently, we are once again dependent on American bark. In this hemisphere there has never been the intensive development of cinchona plantations with emphasis on varieties having a high quinine content. American barks generally have a relatively low quinine content but are reasonably rich in other principal alkaloids. Since all of these alkaloids have antimalarial value it has been decided to utilize American bark in the form of totaquine, which is a standardized antimalarial mixture of the alkaloids. This mixture was recommended by the League of Nations Health Organization in 1932. As now standardized in this country in the present emergency, it contains not less than 7 per cent and not more

than 12 per cent of anhydrous quinine, and a total of not less than 70 per cent or more than 80 per cent of the four principal alkaloids of cinchona. Totaquine, which will be the only form of cinchona available for civilian use in this country, is as effective as quinine sulphate when total daily doses are 20 grains or more. In smaller doses 7½ grains of totaquine have about the same therapeutic effect as 5 grains of quinine. 18,19

ETIOLOGY

The Greeks and Romans, as noted above, from earliest days had associated malaria with bogs and pestilent vapors. In Italy it was a common belief that bad air from marshes was the actual etiologic factor and during the seventeenth century it became customary to say that patients dying from intermittent fevers had died from "the air" (d'aria) or from the bad air (male aria). At first, not the fevers, but the causes of the fevers were referred to in this way. But in time this expression came to be applied to the disease itself. So far as one can determine, Horace Walpole, in 1740, while in Italy, was the first to put the two Italian words together in print as one English word, "malaria," in a direct reference to the fevers of Rome (Oxford English Dictionary).

The word "ague" had been used in England and our own South as a name for the intermittent fevers. It is true that "ague" did not always refer to malaria, but the following reference indicates that it often did. William Grant, in his work entitled, Fevers Most Common in London, printed in 1771, stated (p. 453) that "a true ague is to be distinguished from every other fever by two symptoms; first, the frigus, rigor, and horror febrilis at the beginning of every fit; and secondly, an absolute apyrexia between the fits."

During the nineteenth century the concept of specific pathogenic microörganisms was established on a sound basis and it was natural that men should begin looking for a malaria germ. Because of the long established association between marshes and malaria, scientists began searching in marsh water and marsh air for this elusive pathogen. In Italy, for instance, "human guinea pigs" drank marsh water and allowed it to be injected as enemas or in nasal sprays—without proving anything.

In 1847, Heinrich Meckel, a German scientist, was studying organs and blood from a patient who had suffered from malaria. He noticed in some blood vessels of the brain certain round, ovoid, or spindle-

shaped protoplasmic masses containing black, irregular, pigment granules hitherto undescribed, although Lancisi in 1716 and Bright in 1831 had noted the graphite pigmentation of spleen and brain seen, post mortem, in malaria. From Meckel's carefully worded description it is clear that actually he was looking at pigmented malaria parasites but, at that day and under the circumstances, it is not surprising that he failed to realize their significance.²⁰

Others, including Rudolf Virchow, founder of cellular pathology, also saw and reported this pigment post mortem and it came gradually to be associated with malaria. But no one suspected that the "pigmented globules" were parasitic organisms, although Planer in 1854 had seen them in a drop of fresh blood from a malaria patient.²⁰

In 1876, Doctor Joseph Jones, ²¹ Professor of Chemistry and Clinical Medicine. University of Louisiana in New Orleans, stated that he had been making chemical and microscopical studies of the blood of fever cases for twenty years and that he was able to distinguish clearly the changes induced in the blood by malaria. In fact, he was able in a medico-legal case to testify that certain stains on the coat and shirt of the accused were not paint as suggested but were due to the blood "of a human being who had suffered and was probably suffering at the moment when the blood was abstracted, with malarial or paroxysmal fever." Jones described the characteristic pigment and stated that "many of the particles of the melanemic pigment were spherical, others irregular and angular, some entirely free, others incased in a hyaline mass...." (italics not in original). He was undoubtedly describing malaria parasites.

Laveran

In 1878. Charles Louis Alphonse Laveran, a French army surgeon stationed at the military hospital in Constantine, Algeria, began an investigation of changes produced in the human body by malaria. His attention was naturally directed towards the pigment, now called hemozoin, which had aroused discussion and he searched for it not only in autopsy tissue but also in blood from patients. Working with inferior lenses (he actually used a 4 mm, dry lens) Laveran strained his eye many an hour over objects which did not seem to be normal blood cells but which he could not be sure were parasites. Persistently, he continued his studies and finally, one memorable day, 6th November

1880, in a wet smear of fresh blood, he saw unmistakable waving, hair-like projections or *flagella*, suddenly develop from one of the "pigmented spherical bodies" which had been puzzling him. Now, at last, he was certain that he was observing a living organism, a parasite in human blood. He named it Oscillaria malariae.

Laveran had talent and perseverance to follow up his observation and thus was able to reveal the minute cause of malaria. He saw ameboid, rosette, spherical, crescentic, and flagellate stages, but did not realize the relationship of these forms. Later he wrote four treatises on paludism, between 1884 and 1898, and in 1907 he was rewarded with a Nobel prize for his exceedingly important discovery of the malaria parasite.

Although a colleague, Dr. E. Richard, confirmed Laveran's discovery in Phillippeville, Algeria, in 1882, yet both announcements were received with well-nigh universal skepticism for several years. In 1885, however, Ettore Marchiafava, Italy's leading pathologist, and Angelo Celli, a colleague, saw the parasites in fresh blood behaving as Laveran and Richard had described and they became as enthusiastic in support as they had been in opposition. They were able to sketch, for the first time, part of the developmental cycle and they gave the organism its generic name of Plasmodium. Another Italian, Golgi, also in 1885, observed multiplication of the parasite by asexual spore formation and he noted that the patient's temperature rises when these spores are liberated. Councilman and Abbott, in the United States in the same year, also confirmed the discovery. Then, in 1891, in old St. Petersburg, Romanowski developed a new method of staining blood smears. This has been of the greatest usefulness in all subsequent studies of malaria parasites.

Early Theories

Many years before this discovery of malaria plasmodia numerous observers, "puttering around the springs of science," had suspected that mosquitoes might transmit malaria. For instance, Giovanni Maria Lancisi, a Roman and the greatest Italian physician of his time, in 1717, published a notable treatise on swamp fevers in which he suggested that since malaria disappears after drainage it is due to some sort of poison from marshes, possibly transmitted by mosquitoes. He studied these insects and concluded that they "inoculated their own bad hu-

mours into our blood." Then Lancisi planned a drainage scheme for marshy regions and remarked, "It is better not to fall ill than to be cured."

In 1807, Dr. John Crawford, a native of Ireland, settled in Baltimore, published an article in the Baltimore Observer on the "Mosquital Origin of Malarial Disease." Then in 1848, Josiah Clark Nott, a native of South Carolina, published the suggestion that not marsh vapors but the mosquito of the lowlands was the probable carrier of malarial fevers.

The clearest statement of such speculations was read before The Philosophical Society of Washington in 1882, and published in 1883, by Albert Freeman Africanus King,²² an Englishman who went to America as a boy, studied medicine and practiced for nearly fifty years in Washington. King listed nineteen reasons why he believed that mosquitoes were the real source of malaria. In a footnote he stated that most of his reasons "were quoted from a paper read by Dr. John T. Metcalfe, United States Sanitary Commission, 1862." Metcalfe's article was published in 1863 under the title, "Nature and Treatment of Miasmatic Fevers." Reference to this publication makes it clear that the author brilliantly marshalled a series of basic observations about the epidemiology of malaria. But there is no mention of mosquitoes in Metcalfe's paper. King quoted most of Metcalfe's points and showed how well in each case his own mosquito theory would apply.

As King himself said, "While the data to be presented cannot be held to prove the theory, they may go so far as to initiate and encourage experiments and observations by which the truth or fallacy of the views held may be demonstrated, which, either way, will be a step in the line of progress." The records do not reveal a single experiment resulting from King's paper.

Manson's Theory

Patrick Manson was a Scotchman born in Aberdeenshire in 1844. From 1866 to 1871 he was Medical Officer of the Chinese Imperial Maritime Customs in Takao, Formosa. The next thirteen years of his life he spent in Amoy. China, practicing medicine, still under the auspices of the Customs Service. There he became very much interested in filariasis, a malady common in some tropical areas. While on leave in London in 1875. Manson searched medical libraries to find out what he

could about this disease. He learned that microscopic immature worms called *microfilaria* had been seen by Demarquay in 1863, by Wucherer in 1866 and 1868, and by Lewis (in blood) in 1872. Manson went back to Amoy in 1876, carrying along a new microscope, and he proceeded to study filariasis. It was natural that he should reflect on the question as to how the filarial worm could infect one man from another. He concluded that since the larvae were usually in blood they might escape with the aid of blood-sucking insects. He selected mosquitoes as being most probable because he thought their geographical range coincided with that of the disease.

His theory enunciated, Manson proceeded to feed mosquitoes on patients in whose blood there were embryo filarial worms. He then demonstrated these worms inside mosquito stomachs, where he saw that some were not digested but actually began to develop. Manson succeeded in tracing the filaria through the stomach-wall of the mosquito into the abdominal cavity, and then into the thoracic muscles. During this passage the parasite increased in size, developing a mouth, an alimentary canal and other organs. Quoting Manson, "Manifestly it was on the road to a new human host."

Here at last, scientifically observed, was a parasite of man's blood being sheltered in the gut of a blood-sucking insect, undergoing essential development, "on the road" to another human host. Manifest indeed were the implications of this discovery, first published in 1877 in the China Customs Medical Reports. Manson published again in 1879, using the title, "On the development of Filaria sanguinis hominis, and the Mosquito considered as a Nurse."

A few scientists accepted Manson's report with enthusiasm but many were cold to it, so the observations were repeated and amplified and republished in 1884 in the Linnean Society's Transactions.

Unfortunately, Manson believed that the filarial worms escaped from drowned mosquitoes into-water which then infected the men who drank it. He had placed too much dependence in a book on natural history which stressed the ephemeral character of mosquitoes, leading him to believe that they quickly perished in the water on which they laid their first eggs. The fact that mosquitoes could live for several weeks, repeatedly taking blood and laying eggs, noted by Ross in 1897, was unobserved by Manson. The complete chain of filarial infection from man to mosquito to man was not demonstrated until 1899, when

Low found the worm in the proboscis of mosquitoes. He published in 1900 and his important discovery was soon confirmed by James.

Other scientists had already reported that parasites may in fact exchange one host for another. About 1858, Rudolf Leuckart discovered living in a small water flea called Cyclops, a worm which at one stage of its life is a parasite of fishes. This was probably the first instance when a member of the phylum Arthropoda, to which the insects as a class belong, was seen to be an intermediate host to a parasite of vertebrate animals. Again Leuckart, in 1867-68 observed, in the "meal worm" larvae of certain small beetles, a parasite previously known in the intestines of mice. About the same time Melnikoff, a Russian student working with Leuckart, found that biting lice can act as hosts to dog tapeworms. Here were the first cases known of insects acting as intermediate hosts to animal parasites.

The first time an arthropod was found acting as host to a parasite of man was in 1869 when Fedschenko, a Russian naturalist and traveler, prompted by a suggestion made by Leuckart in 1858, saw in Cyclops some embryos of the guinea-worm which parasitizes man. Fedschenko did not complete the cycle by infecting man again.

Then came Manson, in 1877 to 1879, with his observation which marked the first time an insect (mosquito) had been seen to act as an intermediate host to a parasite (filaria) of man. Manson's observations did not complete the man-to-mosquito-to-man cycle in filariasis but they gave him a logical basis for theorizing about malaria and mosquitoes. He formulated a working hypothesis based on facts observed by himself or published by others. This mosquito-malaria hypothesis he stated publicly in some lectures in 1894 (Brit. M. J., Dec. 8, 1894). Briefly. Manson saw no reason why if mosquitoes could suck worms out of man's blood they might not draw out malaria parasites as well. He had been impressed by seeing in fresh blood smears the same unexplained exflagellation which had been noticed by Laveran. He asked himself, "why should exflagellation occur only after blood is drawn and never in the patient's body?" He surmised that this was for the purpose of infecting some kind of suctorial insect, most likely the mosquito. He thought, as he had about filariasis, that perhaps the mosquito later died, liberating the parasites in water which, when a man drank it, gave him malaria.

Shortly before Manson published his mosquito theory of malaria

transmission, Richard Pfeiffer enunciated in 1892 a logical conjecture of the same sort, based on some of his own studies with a related parasite. Said he, "The following solution suggests itself, but I bring it forward only as a hypothesis, the justification for which rests in the fact that it indicates a line of investigation. It is possible that in the case of the malarial parasite there exists a developmental cycle which completes itself outside the human host, possibly in the body of a lower animal (as, for instance, certain insects). This malarial germ could then be conveyed to man through the air or water or as Robert Koch has remarked to me through the sting of a blood-sucking insect."

So there was nothing fantastic about Manson's hypothesis. But human nature once more asserted one of its most ancient and deathless characters and Manson was derided for his speculations. His critics, some of them men of importance in the scientific world, called him "Mosquito Manson," and once on St. James Street, London, derisively tapped their foreheads as he passed by their club. Manson cheerfully tapped his own at them and walked on to Fame.

Smith and Kilborne's Demonstration

Between 1889 and 1893 Theobald Smith and F. L. Kilborne, Americans, proved the thesis that insect-like creatures can transmit disease from one animal to another. This work was first announced in the 6th-7th Report of the United States Bureau of Animal Industry in 1891, and was published in extenso as Bulletin No. 1 of this bureau in 1893. In some nicely planned, thoroughly scientific experiments, they demonstrated that ticks certainly transfer the cause of redwater, or Texas tick fever, from one cow to another. Ticks, they also found, could even inherit infection from a parent tick and pass it to a cow.

Manson had paved the way by showing that an insect could take an animal parasite out of the blood stream and act as a host to it. He failed to show that the insect could directly infect another man with this parasite. Smith and Kilborne went farther by observing that a specific pathogen could be carried from one animal to another by ticks. Although they appear not to have seen the actual parasite within the ricks, yet their experiments revealed for the first time a continuous chain of infection which included an interlinking arthropod. They were first to demonstrate that an arthropod can be an intermediate host to protozoan parasites of animals.

The Observations of Bruce

In 1896 David Bruce, a British Medical Officer working in Ubombo, Zululand, on a devastating disease of horses and cattle, called nagana, demonstrated, with the aid and comfort of Mrs. Bruce, that tsetse flies can carry the trypanosome parasite from animal to animal. Sheltered only by a wattle and daub hut, living on the roughest of food, sixty miles from other white folk, Bruce and his wife carried out experiments which were clear-cut and convincing. Bruce did not show and, not until 1909 was it demonstrated, that the tsetse fly is a true host rather than simply a mechanical carrier. Yet it seems fair to say that Bruce was the first to prove that a disease caused by a protozoan parasite can be transmitted by a true insect.

Ross's Discovery

In spite of all these advances, no one paid much attention to Manson's malaria theory until there came along Ronald Ross, another Scotchman, and an Army surgeon in the Indian Medical Service. Although Laveran had discovered malaria parasites in 1880, his drawings were not too good and in spite of repeated attempts Ross had not seen the organisms until Manson showed them to him in a London hospital, in 1894. Ross became interested in Manson's mosquito theory of transmission and went back to India to test it by actual experimentation. It seems incredible but there is no evidence that anyone else in the world was actively investigating the mosquito theory of malaria at that time.

Ross tackled the hypothesis seriously, commencing on his birthday. May 13, 1895. After much research, involving many mosquito dissections, Ross in Secunderabad on "Mosquito Day," August 20, 1897, first saw a pigmented malaria parasite from man, growing within the stomach wall of an Anopheles mosquito (A. stephensi?). This insect had fed exclusively on a patient whose blood contained crescents. Ross had no doubt that he was looking at the malaria parasite of man and it was certainly undergoing development in a mosquito. This observation crystallized the mosquito-malaria speculations of centuries!

By this time the fact was well established that multiplication of malaria parasites within red cells in the human body is entirely asexual. It was also known that not all of the young organisms so formed will, upon breaking out of red cells, complete a cycle by splitting asexually

at their own maturity. Some parasites called gametocytes, do not divide in this manner but take on unique shapes so that they may be recognized as distinct from ordinary asexual forms. Those of P. falciparum, for example, look like minute crescents. In 1897-98 William George Mac-Callum, an American pathologist, discovered the significance of these unique forms when he studied exflagellation. He found that the peculiar and sometimes crescent-shaped parasites in malaria blood, which do not split up, are actually male and female cells. MacCallum, in 1897, looking ar Haemoproteus, a malaria-like parasite in a drop of crow's blood, and then MacCallum and Opie at Johns Hopkins in 1898 studying malaria organisms from man, saw male parasites exflagellate and then saw one of the flagella penetrate and thus fertilize a female parasite. There is no evidence that such mating ever takes place inside a living animal, but it may occur in a drop of blood on a glass slide and, as was soon discovered, it usually takes place in a mosquito's stomach. MacCallum and Opie's observations were of great importance for it became clear that malaria parasites have a sexual as well as an asexual cycle, and, taken together with Ross's observation, it was indicated that this sexual cycle probably took place outside the human body in the stomach of a mos-

Soon after Ross had made his first promising discovery in Secunderabad, he was transferred to a place where he was unable to experiment with malaria. This was unfortunate, but finally, through the influence of Manson and others who recognized the great importance of his studies, he was placed on special duty with instructions to investigate malaria in Calcutta. At that time, for various reasons, chiefly because of some riots due to antiplague inoculations, it was not possible for him to experiment with human beings, so, ingeniously, he used birds. In his laboratory he followed the parasite of malaria, stage by stage. in its development in the blood of sparrows. Then he allowed Culex mosquitoes to feed on the birds. Careful microscopic examination of these mosquitoes allowed him to study development of the parasites in the stomachs of the insects. He traced path and growth of the parasite as it made its way gradually from the mosquito's stomach to salivary glands. He then made his greatest discovery, something hitherto unsuspected either by himself or Manson. He found that mosquitoes that had fed on malaria infected birds and that had allowed the parasites to develop and to lodge in their salivary glands, could then infect healthy

birds. These in turn became malarious. So here was the last link! Bird to mosquito to bird. Thus, on July 9, 1898, he completed his demonstration of the entire life cycle of the parasite of bird malaria, which is transmitted by *Culex* mosquitoes. This was Ross's discovery and to no one else belongs the credit. It transcended far beyond Manson's hypothesis and it antedated the Italian contribution.

It was a tremendous and fundamental achievement for it was now perfectly clear that the closely related parasite of human malaria must probably in like manner be carried from man to man by mosquitoes. The first observation by Ross of a parasite of human malaria in the stomach wall of an *Anopheles* mosquito, followed by his absolute proof of the transmission of bird malaria by *Culex* mosquitoes, made it practically certain that mosquitoes transmit human malaria. However, it needed complete proof. Ross, having predicted the probable, set out to prove it. But he encountered initial difficulties and was soon ordered to investigate kala-azar, a subject he had not previously considered. In March, 1899, he left India and a few months later retired from the Indian Medical Service. He completed his original observation regarding human malaria in the same year in Sierra Leone.

The Italian Contribution

Ross, as a matter of course, had promptly reported to the world his work with bird malaria, as well as his original observation of a parasite of human malaria in the stomach wall of a mosquito. His bird experiments were confirmed by several observers, including Daniels, sent to Calcutta for this purpose in December, 1898, by the Malaria Commission of the Royal Society. In November, 1898, Amico Bignami, an Italian, succeeded in infecting a man experimentally with malaria by the bite of an Anopheles mosquito. Bignami and his colleagues, G. Bastianelli and Battista Grassi, a few weeks later, were the first to prove in full the cycle of the parasite of human malaria, and to show that human malaria is transmitted probably by only one genus of mosquito—Anopheles. These findings were quickly confirmed by Koch. In August 1899 the Sierra Leone malaria expedition, of which Ross was a member, found malaria parasites in two species of Anopheles.

To Italian workers must go praise for applying Ross's avian discoveries so quickly to human malaria. It should also be recorded, as noted by Shryock²³ that, just as the work of Theobald Smith and Ron-

ald Ross had stimulated the Italians, so in turn the Italians, through the medium of William S. Thayer, when he returned from Italy to Johns Hopkins, stimulated Walter Reed and his colleagues, who made the next great advance in the field of medical entomology by disclosing the vector of yellow fever.

To Ross is due, for all time, the credit of being first to place a scientific finger on mosquitoes as agents which spread malaria from man to man. This work brought him a Nobel prize in 1902, and later a knighthood from his King.

Dramatic confirmation of the fact that malaria is transmitted by Anopheles mosquitoes was furnished by Manson in 1900 in two simple tests. In the first experiment Doctors G. C. Low and L. W. Sambon and Signor Terzi, all of the London School of Tropical Medicine, lived in a screened hut during the three most malarious months at Fumaroli in the Roman Campagna. It was said at the time that it was sufficient during the fever season to sleep a single night there without protection to contract the disease. Yet these three men escaped. While the fact that they had no malaria was not absolute proof of its mosquito-borne nature yet, because their neighbors in unscreened houses suffered severely from malaria, the experiment was highly suggestive and was reported in scientific periodicals and newspapers throughout the world.

In the second and more convincing experiment, some infected Anopheles were sent by Professor Bastianelli on a three and a half day journey from Italy to London where there was no malaria. These mosquitoes had fed on a malaria patient in Rome. Manson's son, P. T. Manson, a healthy young London student, allowed himself to be bitten by three lots of these mosquitoes and fifteen days later he developed tertian malaria. The experiment was repeated by George Warren, laboratory assistant at the London School of Tropical Medicine. Some mosquitoes were still living after Manson's son fell ill, and, quoting Manson, Warren "thought it would be a pity to waste them, so he fed the insects on his own arm." He came down with tertian malaria fourteen days later. Both volunteers fortunately were cured with quinine. This experiment was significant even to the most skeptical.

TWENTIETH CENTURY-FIRST QUARTER

During the first quarter of the twentieth century it was natural that interest in malaria should be centered around control measures based on the newly demonstrated specific etiology. For malaria control had been an ancient and persistent hope. Records of empirical prophylaxis extend all the way from early centuries in ancient Italy to the late nineteenth century in the United States. For instance, one can cite Nerva, who in 96-98 A.D., was praised for his hydraulic works which improved Roman health because the water of his drains "removed the causes of bad air." Some seventeen hundred years later, still in the empirical age, the transactions of the American Medical Association (1874) were largely filled with a symposium on drainage as related to public health and especially to the malarial fevers. This subject was first explored in the United States apparently in 1832, in the course of a medical survey of New York State. 15

Mosquito nets were mentioned by Herodotus. They have been used ever since to exclude mosquitoes from sleeping individuals. For instance, in the middle of the last century the wife of the first Bishop in Capetown presented a mosquito net to David Livingston when he was in Central Africa. He responded with a charming letter which began as follows:²⁴

14 July 1,863

My dear Lady:

I feel exceedingly obliged by your kindness in making such a beautiful mosquito curtain for me. Beyond a doubt it is the handsomest that ever appeared in this country, and I am a great admirer of the invention . . .

Wire screen cloth for use in excluding mosquitoes and other flies was manufactured in the United States as early as 1865. 15

Larvicides date back to about 1793, when oil (probably whale oil) was used in Philadelphia rain barrels to kill mosquito larvae. Howard, in 1892, was one of the first to use petroleum oil for this purpose. Dust larvicides such as Paris green were apparently not used against mosquito larvae until about 1920. 26,27

The technique of warfare against mosquitoes developed rapidly after Ross disclosed the fundamental etiology. Indeed, Ross himself in 1899 in Sierra Leone carried out the first antimalarial work based on his own discovery. It is notable that Ross later wrote: "My work had been done not at all for the sake of parasitology, but in order to find a method for reducing the incidence of malaria amongst the inhabitants of warm countries." His prime interest remained, to the end, malaria control.

Outstandingly successful antimalaria projects in the first quarter of the century, included besides those mentioned below, that initiated in Malaya in 1901 by Malcolm Watson, that by Oswaldo Cruz and Carlos Chagas in Brazil, and by Ronald Ross in Ismailia, to mention only three of many.

Staten Island

At the turn of the century Staten Island was not only malarious, but also had an uncomfortably high density of pest mosquitoes. In 1901, Dr. Alvah H. Doty, Health Officer of the Port of New York, found that in one section of Staten Island 20 per cent of the inhabitants had malaria. He also discovered that the problem was twofold—pest mosquitoes breeding in salt marshes and *Anopheles* mosquitoes breeding in collections of fresh water, inland. Doctor Doty himself one evening collected twenty-two mosquitoes in a house, and found more than half to be anophelines, while on the opposite corner there was a patient with acute malaria.

A fairly large-scale antimosquito campaign was planned and carried out effectively in Staten Island under the direction of Dr. Doty and with help from the Department of Health of New York City.²⁸

Although there is no reference to this project in Winslow's biography of Biggs, the following statement has significance: "The New York City Health Department [of which Biggs was General Medical officer] from 1902 to 1913 was in large measure the concrete expression of the mind of Hermann Biggs; and the history of its development is the history of the progress of his sanitary statesmanship." It is also made clear in this biography that Doty and Biggs were close friends (indeed Doty was best man when Biggs married in 1898). Therefore, it seems not unreasonable to suppose that, in this Staten Island malaria and mosquito pioneer control project, one of the earliest, and one of the most effective of the early campaigns, in the United States, inspiration and advice stemmed from the great sanitarian we are honoring tonight—Hermann Michael Biggs.

Except for this work in Staten Island, and in one or two other areas, as in New Jersey, Long Island, and California, this country was slow to react until the Panama project had dramatized the subject of malaria control. Intensive malaria control in the South began with practical demonstrations in 1912-1916 in North Carolina, Virginia, and Missis-

sippi by Henry R. Carter and R. H. von Ezdorf of the U. S. Public Health Service, and, in coöperation with the International Health Board, at Crossett, Arkansas, in 1916.

During the World War in 1917-18 the Public Health Service carried out an extensive extra-cantonment, and the Army an intra-cantonment antimalaria program in fifteen states over a total area of 1,200 square miles. This very successful project not only protected considerable numbers of troops but it also demonstrated malaria control in a practical way and resulted in the training of a large personnel. In the years from 1919 to 1922 The Rockefeller Foundation, coöperating with the Public Health Service, demonstrated that malaria control in the South could be done for from 75 cents to a dollar per capita, with maintenance costs of 25 cents a year, about one quarter of the average yearly malaria payments per capita for quinine, doctors, and undertakers. These experiments proved that malaria control by antimosquito measures in the South was not only economically feasible but a sound business proposition.

Gorgas

The greatest early twentieth century demonstration of the usefulness of mosquito control measures was furnished by William Crawford Gorgas, who like Laveran, Bruce, and Ross, was an Army medical officer. In the words of Sir William Osler, "There is nothing to match the work of Gorgas in the history of human achievement." Not only did Gorgas completely control yellow fever by anti-Aedes measures (following the work in Cuba of Finlay, and of Walter Reed and his colleagues, which disclosed the vector of epidemic urban yellow fever) but, as the result of his Anopheles control, the malaria rate in Havana was reduced from the figure of 909 per thousand in 1899, to 151 in 1901, 44 in 1904, and 19 in 1908.

Because of his outstanding success in Cuba, it was natural that medical authorities should suggest that Gorgas take charge of sanitation during construction of the Panama Canal, where yellow fever and malaria had turned engineering efforts into shambles. Mosquitoes, at that time not yet unmasked, had administered to man the greatest engineering defeat ever known. The French losses in eight years were over 200 million dollars and 50,000 lives!

When the United States undertook to build this canal, Gorgas was

put in charge of the Sanitary Department of the Canal Zone by The Surgeon General of the Army. He was aided by an exceedingly capable Chief Sanitary Inspector, Joseph A. Le Prince, by the brilliant laboratory studies of Samuel Taylor Darling, and by the outstanding assistance of Henry Rose Carter, of the U. S. Public Health Service.

The Anopheles carrier in Panama bred in ponds, marshes, swamps, and standing water. The problem of controlling this widespread rural insect was much greater than that of controlling Anopheles breeding in Havana. The malaria rate in the Canal Zone in July, 1906, was equivalent to 1,263 hospital admissions per year per 1,000 of population! But Gorgas, with his unusually efficient sanitary organization and inspectors, reduced the numbers of canal workers admitted to hospitals for malaria from a yearly rate of 821 per 1,000 in 1906 to 76 per 1,000 in 1913. This work by Gorgas, with his concomitant success against yellow fever and dysentery, was a superb accomplishment, described by Sir Malcolm Watson as "the greatest sanitary achievement the world has seen."

If it be assumed that without Gorgas and his sanitary victories the occurrence of disease among our employees would have paralleled that among the French employees, who were without such help, then it can be stated that Gorgas saved the United States some 39½ million mandays of illness between 1904 and 1914, and not only so but he prevented some 71,000 deaths in the ten years of canal construction. Gorgas himself estimated that the sanitary work on the isthmus during the ten years of construction saved the United States some 80 million dollars, if indeed the canal could have been built at all in the presence of such intense malaria and yellow fever as that experienced by the French.³⁰

It is easy to forget and time rapidly dims even the brightest records. Hence, it does not seem amiss to recall once more the tremendous world-wide impression made by the sanitary victories in Havana and Panama. For instance, when Gorgas visited London in 1914 he received, according to Osler, the greatest ovation ever given a medical man in England. Oxford University held a special convocation to confer upon him the honorary degree of Doctor of Science. At home, the President made him Surgeon General of the Army, and The Congress about a year later made him a Major General, at that time an almost unprecedented rank for a medical officer. He served his country with distinc-

tion in this high office during the World War. After retiring from the army in 1918, at the age limit, he went to South America as director of a yellow fever commission, under the auspices of The Rockefeller Foundation.

In 1920, in London, Gorgas became ill and was taken to the Queen Alexandra Military Hospital. There he was knighted by George V, receiving from the King's hand the insignia of Knight Commander of the Most Distinguished Order of St. Michael and St. George. A few days after receiving this knighthood, Gorgas died and was given the funeral of a British Major General in St. Paul's Cathedral, the highest honor that Britain could bestow. Later, his body lay in state for four days in Washington, and at the Church of the Epiphany an illustrious assembly gathered to pay last respects to this man whom the Lancet called "the best known and most uniformly successful medical administrator not of his age alone but of any age."

THE PRESENT

In this second quarter of the twentieth century malariology has shared in the general advance of science. It is not possible here to do more than to cite three notable lines of progress.

The Synthetic Antimalarials

Paul Ehrlich found, in 1891, that methylene blue will stain malaria parasites and he hoped that it would therefore act therapeutically by damaging the parasites in human blood. When its chemotherapeutic action was found to be slight, investigators modified its chemical structure, hoping to enhance the plasmocidal effect. This line of study finally led by devious paths to the synthesis of plasmochin, in 1924, by Schulemann and his colleagues in Germany, and of atabrine in 1930 by Kikuth, Mietzsch and Mauss in the same place. Neither of these drugs is synthetic quinine. Plasmochin is a quinoline derivative. Atabrine is a yellow dye derived from acridine. Plasmochin was found to be unique in its effectiveness against gametocytes, especially those of P. falciparum, and in its relative ineffectiveness against the schizonts of this same species. Atabrine was found to resemble quinine in its action against all species of schizonts and in its weakness in affecting any of the gametocytes. Quinine, plasmochin, and atabrine are alike in their inability in a percentage of cases to cure without the occurrence of relapses,

and in their failure, in safe doses, to prevent infection by sporozoites. None of the three has been found to be a true causal prophylactic, although each in small doses tends to suppress clinical symptoms. All three may exhibit toxic effects, quinine least and plasmochin most often.

Atabrine is by no means a perfect substitute for quinine but it is, nevertheless, a fairly effective antimalarial, now (fortunately) being manufactured on a large scale in the United States, England, and Russia. The Germans also are using extensively tablets of their own manufacture.

There is still no drug which is sufficiently effective to justify the use of chemoprophylaxis to eradicate malaria from communities. However, in spite of the fact that neither plasmochin nor atabrine has proved to be that potent chemical wand so earnestly desired, yet these drugs do represent a notable forward step in malaria therapy.

Pyrethrum Spray-Killing

There is a chrysanthemum indigenous to Dalmatia, growing in the fields like a small yellow daisy. The full blown flower of this plant contains active principles, called pyrethrins, which are deadly to insects. This latter fact has been known for many years in agriculture and public health and the dried pyrethrum flowers have become an important item of trade, so that large pyrethrum plantations have been developed in Japan, Kenya, and lately, in India.

Pyrethrins are contact poisons to which the cuticle of a mosquito is permeable. The toxic effect is seen chiefly in a destructive action on the central nervous system.³¹ Kerosene extracts of pyrethrum have long been in household use against mosquitoes but only recently has it become apparent that pyrethrum spray-killing in many rural tropical areas is the best weapon available for malaria control, in fact it is the only one which is financially feasible in much of the rural tropics. Standard use of larvicides or of drainage and filling, or of screening has been far beyond the pocketbooks of these areas.

If the adult malaria-carrying mosquitoes of a community can be destroyed before they have lived long enough to become infective then malaria transmission in that community ceases. In villages where the malaria vector mosquito species tends to remain inside huts, cowsheds or outbuildings accessible to spray-killing, it is possible by spraying thoroughly once a week with pyrethrum to break the chain of infection and

thus to control malaria, at a cost which is considerably less than the cost of malaria and is not beyond the economic potentialities of the tropics.

This is notable progress which may be further enhanced by newer methods of dispensing the spray.³² In 1935 it seemed true to state about the tropics that, "so far as average rural areas are concerned, the problem of control is still unsolved . . . it appears that we have no economically feasible control measures."³³ In 1942, experiments in rural South India proved that the malaria chain can be broken, in typical small villages, at per capita costs around \$0.08 per year, which are economically feasible even in India.³⁴

Species Eradication

In 1930, Shannon, an entomologist on the staff of The Rockefeller Foundation, reported that he had found Anopheles gambiae in Brazil. This was of great interest because gambiae is a notorious African species. Apparently a fast French destroyer had taken this deadly mosquito from Dakar to Natal, and the stowaway had succeeded in colonizing in the New World.

By 1931 the species had spread 115 miles up the coast stimulating local antimalaria campaigns along conventional lines. These had some success and lulled the Health Department into a sense of complacency which was completely shattered in 1938 when gambiae caused what was probably the greatest epidemic of malaria ever seen in the Americas. During the first six months there were over 100,000 cases with at least 14,000 deaths. It became apparent that the African invaders had colonized for more than 200 miles north and west of Natal. This African species threatened to invade all of northern Brazil from which it might push on into Central America, with devastating results.

Displaying great courage, the Brazilian Government decided to attempt not merely the usual antimalaria measures but an actual eradication of every gambiae mosquito in the country. This complete extirpation of a species of mosquito had never been accomplished in any land at any time. A poll of experienced malariologists would doubtless have judged it an impossibility, for gambiae has the habit of breeding in all types of water collections, large and small.

By presidential decree, in 1939, the Malaria Service of Northeast Brazil was created. It was organized as an anti-gambiae rather than anti-malaria service. Under the guidance of Soper and Wilson, of the staff of The Rockefeller Foundation, this Brazilian organization, much of which had had years of training in anti-Aedes work, grew to be 4,000 strong, and was allotted total budgets of more than two million dollars. The whole infested area, and a little beyond, was divided into squares of workable size; an adequate control gang was assigned to each square; and there was simultaneous and meticulous application of Paris green to breeding places and of pyrethrum spray-killing to adult resting places. The result of this determined, systematic and overwhelming attack was what now seems almost certainly to have been the complete eradication of gambiae from northeast Brazil and thus from the New World. The last evidence of gambiae in this area was found on November 14, 1940. Since January, 1941, all anti-gambiae measures have been suspended; a large staff of trained men have been constantly combing the area and contiguous zones for gambiae, and there has been a standing cash reward for finding it. Not a single living gambiae larva or adult could be found in 1941 or 1942. (But some dead adults were found in an airplane from Africa in 1942, illustrating clearly the need for complete enforcement of the pyrethrum spray-killing regulation for all airplanes arriving in Brazil from Africa.)

This is a very great achievement, a sanitary triumph, which marks the start of a new era in the fight against malaria. Great though the cost of the Brazilian campaign, it was very much less than the toll which gambiae would have exacted in the long run had it been only curbed by usual antimalaria measures rather than extirpated by a new and bold technique. This success suggests similar possibilities in other parts of the world. It is no longer certain that the malaria-carrying mosquitoes of a country could never be exterminated.

With large numbers of men well-trained in mosquito and malaria control work returning from overseas after the war, with the need for progressive post-war public health planning, with a genius for organization, and with money, it is certainly within reason to believe that malaria, if not the last mosquito vector, could be eradicated from the United States.

THE FUTURE

There are certain trends in malaria research which may be taken as some indication of what the future may bring.

Antimalarials

For instance, there is a tremendous amount of chemical, pharmacological, and clinical research going forward at the present time in a determined and intensive search for an antimalarial chemotherapeutic agent which will not have the deficiencies of quinine, plasmochin, and atabrine. The need is apparent when it is recalled that not one of this trio will cure with certainty, not one is a true prophylactic drug, and not one is of much value in the control of community malaria. Clark and his colleagues³⁶ as an experiment, tried for ten years to control malaria in some Panamanian communities by means of these drugs. They concluded that it was impossible by mass treatments to reduce the parasites to a point where malaria transmission in a community was much lessened.

It seems reasonable to hope that a more effective antimalarial will be developed in the not too distant future.

lmmmenity

As the science of immunology develops it is probable that the immunity factor in malaria will assume more importance. Whether vaccines and serums will ever have a practical place in combating malaria is a matter for speculation, with some evidence that some day a way may be found to make them useful.^{37,38}

Removal of Social Obstacles

Probably the greatest advance in the future will be the removing of some of the social obstacles which block rapid progress in malaria control. Surely, it is amazing that, with all of our laboratory and field knowledge of malaria and its anopheline carriers, with all of our potent weapons of oil and Paris green, screens and pyrethrum, drainage and water-manipulation, with brilliant examples of successful projects, with our repeated demonstrations that it is cheaper to control malaria than to pay the economic toll it exacts from its victims—with all this, malaria control in the middle period of the twentieth century is still such a feeble effort. Is this due to insufficient knowledge, inefficient tools, paucity of funds? Or is our social organization unable to apply effectively the money, potential labor, existing weapons of control, and wealth of experience and research findings?

The answer to the question, "Why malaria?" seems to involve certain social obstacles to malaria control. Over widespread areas, particularly in the tropics, these appear to consist of such social facts as (1) a fundamental absence of educated and effective public opinion as regards the economic importance of malaria, the methods available for its control, and the community's responsibilities for its prevention; (2) a surprisingly limited use of sound administrative principles in public health, so that coördination and coöperation between departments does not exist, and continuity of effort in dealing with malaria is rare; (3) a lack of sufficient numbers of personnel specially trained in the entomological, agricultural, engineering, and public health phases of malariology; (4) a lack of cognizance by public officials as to the cost of malaria and the public benefit to be derived from its control; (5) a widespread ineptness in applying effectively and practically the results of research in malariology.³⁹

What Bernal⁴⁰ wrote about science in general may be said of malaria control: "The obstacles to the solution of the problem are not any longer mainly physical or biological obstacles; they are social obstacles." It seems incredible that malaria still can be so great a scourge, for it is a preventable disease regarding which we possess as complete knowledge as for any human malady. The literature on malaria stretches back 2,000 years, grows actively, and has become enormous. There have been devised potent weapons for treatment and control. But malaria persists, of all diseases today probably the most effective barrier to prosperity, contentment, and health. What a paradox! Man, with his incredible machines and his streamlined science, stricken each year in millions because he fails to outwit a mosquito carrying Death in its spittle!

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BRUCELLOSIS*

Diagnosis, Differential Diagnosis and Treatment

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some aspects of brucellosis is a welcome one. That there are few subjects so neglected or so worthy of attention is slowly coming to be realized. What is needed however protean manifestations and numerous disguises. I cannot hope to give it to you fully in the necessarily limited time that is available, for it is not a small subject, even when restricted to diagnosis and treatment.

I am indebted to my superior officers in the Navy Department for their sufficient interest in scientific medicine to permit me to interrupt my tour of sea duty long enough to address you. This action does not imply official approval of the subject matter. The ideas expressed are my own and do not necessarily reflect those of the Medical Department of the Navy.

INDICATIONS FOR LABORATORY STUDIES

In deciding when it is necessary to employ the various diagnostic procedures for brucellosis in the study of an obscure illness the question of exposure is one that may well be, to a large extent, ignored. Brucellosis cannot be ruled out on the basis of lack of known exposure. Indeed, exposure to Brucella infection is comparable in its universality to exposure to tuberculosis. There are few persons who have never ingested raw milk or cream, or raw milk products, such as cheese, butter, buttermilk, or ice cream, or who have never been in contact with infected cows, horses, sheep, goats or hogs.

In children it is relatively easy to trace the feeding formulae in infancy, the subsequent diet and the contacts. If the child never had mother's milk, nor raw nor imperfectly pasteurized cow's or goat's

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milk; if it had none but pasteurized milk products; if it never came in contact with possibly infected animals—and if the story can be completely credited—then that child's exposure is unlikely. The use of certified milk exclusively, unless it is pasteurized, is no guarantee against milk-borne infection, however, for certified milk is not above suspicion if raw. The possibility of intrauterine infection or infection during passage through the infected birth canal of the mother cannot be dismissed lightly. Hagebush and Frei found in 74 per cent of 182 cases of child-hood brucellosis, that the mother also had the disease. This might have been due to a common milk supply; however, four of the infants developed relatively severe symptoms and positive tests before nursing and before taking any other food except dried or evaporated milk formulae. Illness developed in from three to eight days after delivery. Similar instances have occurred among my patients and have been reported by others.

That Brucella grows more readily in cream than in milk is often overlooked in considering exposure. Patients often remark that they never use milk, but cream is almost universally used. Contact with cattle and other possibly infected domestic animals must also be considered. The laboratory worker must be classed among those exposed by direct contact, along with farmers, butchers, slaughterhouse employees and vererinarians.

It is not only the rural resident who is exposed through the medium of raw milk. There is a smug complacence among laymen and physicians alike, when the diagnosis of possible brucellosis is made in a patient who has been a lifelong resident of New York for example. The suspicion is likely to be dismissed as fantastic because the patient has used pasteurized milk and cream at home exclusively for the past twenty-five years, feeling that this somehow gives security against Brucella infection. There are but few of these persons who have not spent summers or brief vacations in the country where, knowingly or unwittingly, they have had raw milk. About 45 per cent of the herds in the United States have showed some degree of infection.

The death from acute brucellosis of a New York physician a few years ago illustrates the need for considering this infection in the absence of any known history of exposure. Just before death Brucella melitensis was recovered from a blood specimen. Then, as the result of keen thinking on the part of one of the attending physicians, the same

goat strain of Brucella was grown from an uneaten portion of Italian cheese found in the patient's apartment. Cheese had always been looked upon as innocuous.

Incubation period gives little or no help in diagnosis of infection as related to known exposure. The elapsed time from a single known exposure until development of evidence of active illness has been noted to be anywhere from a few days to several months. Even this is understatement, for clinically recognizable illness may not occur for years following exposure, the infection remaining latent or subclinical or subsiding to a chronic phase after a wrongly diagnosed acute illness.

It is therefore better to leave the question of exposure until later in the study of the patient and not to be influenced greatly by it; to consider the possibility of brucellosis and to do the various tests routinely in all obscure illnesses, acute or chronic.

My plea for more accurate diagnosis of this common illness would be bolstered if I could give you exact figures as to its incidence; as, for example, what percentage of all admissions to a large general hospital is represented by Brucella infection. At some later date I hope to gather this information through a study of naval personnel and their dependents. Gould and Huddleson estimated that about 10 per cent of the population of the United States had become infected and that about one per cent of that number were clinically ill. The incidence of infection is higher in rural communities but, if one is brucellosis-conscious, the evidence of its frequency among all groups is overwhelming. In the course of the last ten years of a practice largely devoted to internal medicine and consisting of urban and rural dwellers in about equal proportions, approximately 400 cases of brucellosis were encountered. Of these about 30 per cent were residents of New York and the metropolitan district. About 10 per cent were acute cases, the remainder chronic. For the previous ten years I had failed to recognize a single instance, having shared the usual impression that it was an acute illness of infrequent occurrence characterized by long-continued high fever, and diagnosed by the simple expedient of the blood agglutination test. In 1941, during my first six months of naval service, fourteen cases of brucellosis were diagnosed on my wards at the Brooklyn Naval Hospital. These were the acute infectious disease wards and therefore did not include the cases presumably admitted to other wards.

These are but some of the reasons for doing routine tests for brucel-

losis. Let us now consider the methods and the rationale for the performance of the multiple tests rather than place reliance on the blood agglutination test alone.

DIAGNOSIS

There are four commonly used laboratory procedures: blood agglutination test, intradermal test, phagocytic index, and culture. The use of these tests, along with careful history and physical examination, usually furnishes adequate evidence on which to establish or rule out the diagnosis of brucellosis.

The Agglutination Test: This test is comparable to the agglutination test with B. typhosus. It is often negative in acute brucellosis however, and, in a probable majority of cases, is negative in the chronic illness. Therein lies the most frequent source of error in the diagnosis of brucellosis, next to the failure to consider the diagnosis at all. Most unfortunately it is almost standard practice to accept one or more negative blood agglutination tests as signifying the absence of Brucella infection.

To evaluate agglutination in a low titer (below 1:80) as negative is also wrong. Such results should be viewed as suggestive, pending further study. The absence of agglutinins does not mean the absence of infection. Positive blood culture, in the presence of persistently negative agglutination tests, has been reported by Evans and others. This cannot be emphasized too strongly.

The finding of Brucella agglutinins in low titer occasionally occurs as cross-agglutination due to infection with B. typhosus, B. tularense, or B. proteus X 19. Differentiation is usually easy through completion of the other laboratory procedures applicable to the various infections as well as for brucellosis. In tularemia, for example, agglutination may occur with Brucella abortus in a 1:20 or 1:40 dilution of the patient's serum but usually occurs in a higher dilution with B. tularense.

The presence of agglutinins in a titer of 1:80 or higher is presumptive evidence of Brucella infection, if occurring in a patient whose clinical findings are compatible with brucellosis. Agglutinins may persist for weeks or months after recovery but usually are fleeting.

Parenthetically I should add that negative blood agglutination tests in cows likewise are unreliable evidence of the absence of Brucella infection. Positive cultures of the milk of cows with persistently negative blood agglutination tests have been reported by several. It is for this

reason that I believe that certified milk should also always be pasteurized

As evidence of the still-existing misconception of the significance of the blood agglutination test, as well as of too great faith in the likelihood of positive culture, I quote the following from Stitt: "Undulant fever obviously may be differentiated from trench fever by the detection of Micrococcus melitensis in the blood or by the agglutinating reaction of the blood with the organism." We are to understand from this that brucellosis is ruled out if culture and agglutination test are negative. To discuss agglutination test and culture for Brucella infection without mentioning the limitations of the tests is to add to the confusion already existing. It seems essential to add the qualification, "if positive," to a mention of either test since neither has any significance when negative.

It is essential to collect specimens of blood for the agglutination test prior to the performance of the skin test lest artificial agglutinins be formed in response to the intradermal antigen.

Phagocytic Index: Huddleson gave the name opsonocytophagic test to this procedure for the determination of the specific phagocytic power of the white cells, adapting the method to Brucella infection from technique in use in the study of other illnesses. Much controversy has arisen over its value. It has proved to be highly accurate in my work, both in diagnosis and as a criterion of progress in patients under treatment, although it has limitations. By itself it has little significance, which is surely what Evans meant when she said that it has the least value of the four accepted laboratory procedures. Her comment has been interpreted by some to mean that it is unreliable. When properly performed, on freshly collected blood, with meticulous technique, and when interpreted in the light of the result of the intradermal test and of clinical findings, it will be found to be invaluable. Performance of the test may be deferred for a week or even ten days after the skin test when circumstances make it necessary, without materially affecting the result.

The result may be reported as the numerical index of Foshay, graphically, as by Evans, as the percentage of cells showing marked phagocytosis, as the average number of bacteria contained in each white blood cell, or as the number of cells showing marked, moderate, slight and no phagocytosis, in accordance with Huddleson's method. This last method seems to me most informative; also the shift to the right or

left is easily visualized in comparing subsequent reports. The test should not be thought of as positive or negative but rather as showing high, moderate, little or no resistance.

In itself the phagocytic index indicates only the degree of opsonic activity of the blood toward Brucella. When accompanied by a positive skin test it does help greatly to distinguish between patients who presumably have recovered from old infections and those whose present illnesses are probably due to still active infection. The skin test, to be discussed shortly, must be performed before the diagnostic significance of the phagocytic index can be evaluated. If the skin and agglutination tests and culture all are negative we do not know whether or not the patient has ever had brucellosis and therefore the opsonic power of his white cells has no interpretable diagnostic significance.

If the skin test is positive we know that the patient has an old or a recent infection, of undetermined activity. If then we find a low phagocytic index, it is presumptive evidence that the patient has not recovered from that infection. If the positive skin test is accompanied by a high phagocytic index, it is presumable that the patient has recovered from that infection. Obviously, this information cannot be deduced in the absence of illness possibly referable to Brucella infection.

The test may not be interpreted to indicate cure or immunity, no matter how high the index, contrary to Huddleson's belief. Robinson reported the case of a patient who died of brucellosis with 100 per cent of his white cells showing marked phagocytosis; the blood culture was positive. The relative virulence of the organism must be considered. Also, what may appear to be immunity may change to a low level of resistance preceding or accompanying relapse within a few weeks, for opsonins, too, may be fleeting. So, in a small percentage of patients, the test is not helpful.

Blood for the opsonocytophagic test must be fresh. In my monograph I quoted Huddleson as stating that the procedure must be done before the blood is more than six to ten hours old. Lintz has subsequently pointed out that the phagocytic activity of the white cells decreases rapidly after the first or second hour. Therefore the test should be done on blood that is not more than three hours old.

The Intradermal Test: Use of a sensitive antigen and accurate interpretation of the skin reaction obviously are essential. Heat-killed Brucella abortus organisms seem to furnish the most sensitive and reliable

antigen. Brucellergin, derived from the filtrate of the three strains of Brucella, apparently is much less sensitive. In a series of tests in 168 patients, all of whom had drunk milk from an infected herd, Angle did intradermal tests with the heat-killed organisms on one arm and with Brucellergin on the other, simultaneously; he noted fifty-four positive reactions to the heat-killed vaccine and only twenty-seven to Brucellergin. Although he made no comment on its significance, other than to point out that the possibility of a slough at the site of the test is avoided by the use of Brucellergin, it is obvious that the question of sensitivity of the antigen is involved.

The test is done with 1/10 cc. of a killed bacterial suspension of 2000 million Brucella abortus organisms per cc. injected intradermally with a very fine, short needle, using the same technique as for the tuberculin test. The reaction should be read at the end of four days but, if apparently negative, should be kept under observation for another seven days. I first pointed out the importance of the delayed positive reaction in 1934; the observation has since been confirmed by others. A positive reaction may vary from a visible, palpable, reddened nodule at the site of the intradermal injection to a markedly reddened, indurated area with lymphadenitis and marked systemic reaction.

A weakly positive reaction has the same diagnostic significance as a violently reacting test. Both indicate that the patient at some time harbored or suffered from Brucella infection. The degree of local and general reaction, in addition, indicates the degree of sensitization to Brucella protein that has occurred. This is an aid in planning vaccine therapy when such is indicated. Also, the aggravation of existing signs and symptoms, clinically attributable to the illness, which so commonly occurs during the skin reaction, is of additional diagnostic significance. This is especially valuable information if, following the subsidence of the skin reaction and the clinical exacerbation, there is evidence of clinical improvement and a commensurate rise in the phagocytic index.

It is well to avoid the mixed strains present in commercial vaccine in doing the intradermal test, as well as in treatment. Most of them comprise abortus and melitensis or abortus and suis strains. They are no more accurate than the abortus strain alone, no matter what the infecting strain of Brucella, but are more apt to produce severe reaction, local and general, and a greater percentage of sloughs. The necrosis

occurring at the site of the intradermal injection in a small percentage of patients will be shown, along with various types of skin reactions, by means of a few kodachrome transparencies. The sloughs may be slow to heal and may leave some permanent scar but the information obtained is of sufficient value to justify use of the method.

A positive skin test alone should never be the sole evidence on which to base a diagnosis of brucellosis. Nor may a negative skin test be used to rule out brucellosis; positive blood cultures, in the presence of negative skin tests, have been reported by several.

The presence of positive skin tests in seemingly well persons has been quoted as evidence of the non-specificity of the skin test. That is, I believe, an inaccurate evaluation. Under such circumstances the finding is comparable to a positive tuberculin test in a well person, indicating old infection, quiescent or possibly actually cured.

Culture: The discussion of culture is left until last, not because of its lesser importance, but because it is the least likely of the four tests to furnish any positive information, especially in chronic brucellosis. It is the one definitive diagnostic measure, when positive, just as tubercle bacilli in the sputum furnish the only certain evidence of pulmonary tuberculosis. The various tests for brucellosis all must be correlated with each other and with the clinical picture, as I have reiterated deliberately. In the absence of positive culture from blood, urine, feces, sputum, bile, synovial fluid, or other exudate, discharge, or tissue, we may not rule out brucellosis until all other diagnostic and clinical study has been made. The cultural methods must be exact. It is only in the presence of acute infection, especially with the melitensis strain, that there is reasonable expectancy of recovering the organism, so difficult is it to grow. Although methods of culture have been improved, there seems little tendency on the part of laboratories to utilize these more accurate methods. Poston's technique includes the use of special media (liver infusion agar, bacto-tryptose agar, and others), the use of 5 to 10 per cent of carbon dioxide in air for the growth of the abortus strain, long weeks of incubation and transfers, and the keeping of inoculated guinca pigs for periods as long as eighteen weeks before studying them at autopsy. Poston studied fourteen patients in whom she suspected chronic brucellosis in spite of the completely negative multiple tests. Using her own technique she isolated Brucella from five of the fourteen patients.

The fact that cultural findings are usually negative should not dis-

courage their use, along with the other tests. In fact it should be a routine procedure in the study of all patients in whom brucellosis is suspected and in all other illnesses of an obscure nature. By way of example I will briefly quote the case of a young married woman who had three spontaneous abortions, with salpingitis and profuse purulent discharge accompanying convalescence from each abortion. Fever never was above 99.6. Blood agglutination with Brucella abortus occurred in a dilution of 1:40. I did not see her following the first occurrence. At the second abortion the placenta showed large areas of necrosis but was inadvertently destroyed before culture could be attempted. The placenta at the third abortion showed gross and microscopic areas of calcification but no significant cultural findings, perhaps due to the long delay in transit to the nearest good laboratory. Following this occurrence a specimen of uterine discharge, obtained from cervix and vagina by aspiration, after instillation of sterile glycerol, was sent by mail to the New York State Department of Health Laboratory, 135 miles distant. In spite of the delay, Brucella of the abortus-melitensis group was isolated.

Ordinarily it is essential that specimens for culture be very fresh, not more than an hour old, if cultural attempts are to have their best chance of success. It is too often the habit of laboratory technicians to allow specimens to stand about for hours before inoculating the proper media. In one instance a specimen of bile, obtained by duodenal drainage after considerable difficulty, was not sent to the laboratory until the next morning, but an utterly valueless report of no growth of Brucella was rendered in the routine way. I might add that at least a degree of enthusiasm for the work in hand seems particularly important in the study of brucellosis.

DIFFERENTIAL DIAGNOSIS

Brucellosis is becoming known as a disease which masquerades under as many guises as does syphilis. Its differential diagnosis obviously involves consideration of the innumerable diseases and syndromes which it is so apt to simulate. There will be time for discussion of but a few.

Pulmonary Tuberculosis: Pulmonary tuberculosis is one of the illnesses most frequently confused with brucellosis. Clinically, chronic or subacute brucellosis may so exactly simulate pulmonary tuberculosis that the patients are admitted to sanatoria without hesitation on the part

of staff examiners. If sputum is negative, if x-ray evidence is lacking or if there are atypical lesions, a presumptive diagnosis of tuberculosis is often made on the basis of productive cough, loss of weight, pleuritic chest pain, night sweats, fatigue, afternoon elevation of temperature, positive tuberculin test—and failure to consider brucellosis. Loss of weight, low grade fever and fatigue are, of course, very common in brucellosis. Occasionally the pulmonary lesions of brucellosis are indistinguishable from tuberculosis. Pleurisy is fairly common. Beatty has reported several instances of hemoptysis in brucellosis. If the multiple tests for brucellosis are done, most of the errors are avoidable. The coexistence of the two diseases presents a most complicated problem and is not infrequently encountered.

The chagrin of the superintendent of one of the best of the tuber-culosis sanitoria at the reply made by a patient will probably be long remembered by all present. He had just completed the chest examination of a young woman at a follow-up clinic. "My dear girl," he had said, "you do not have tuberculosis. Whoever made such a diagnosis?" The patient had answered, "You did, Doctor. I spent six months in the sanatorium under your care." He had forgotten that he had made a clinical diagnosis of tuberculosis himself and had admitted her in spite of negative sputums and only suspicious radiographic findings. She had had a severe productive cough, pleuritic pain, low-grade fever, weight loss and secondary anemia, subsequently shown to be due to brucellosis during one of several exacerbations which followed.

A normal or low sedimentation rate, when present, is of great help in the differential diagnosis between active tuberculosis and brucellosis. In a small proportion of cases the sedimentation rate is also increased in brucellosis, however.

Peribronchial and hilar infiltration may be seen on routine chest x-ray in suspected tuberculosis. If associated with clinical and laboratory evidence of brucellosis and no evidence of tuberculosis; if there is found complete clearing at subsequent x-ray examination, with later recurrence accompanying relapse of brucellosis, there is adequate evidence that these are respiratory manifestations of brucellosis. Figure 1 illustrates this point. One young man had a recurrence of orchitis and epididymitis with each exacerbation of brucellosis which was also attended by lung involvement, with complete resolution between attacks.

Pneumonia: Figures 2 and 3 of two patients with lung involvement.

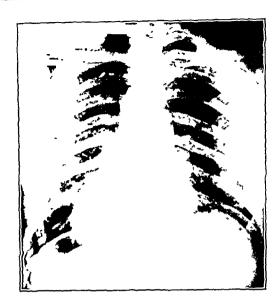


Fig. 1. Infiltration, middle third of left lung, during subacute relapse five years following severe, prolonged, typhoid-like Brucella infection. Orchi-epididymitis accompanying this and subsequent recurrences of pulmonary involvement, each attack subsiding promptly following specific vaccine therapy.

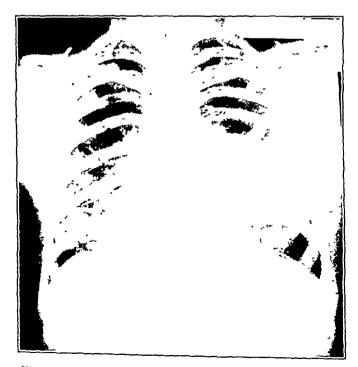


Fig. 2. Brucella lobar pneumonia in Maltese sailor; history of brucellosis in childhood; signs and symptoms similar to lobar pneumonia of other origin; slow resolution.

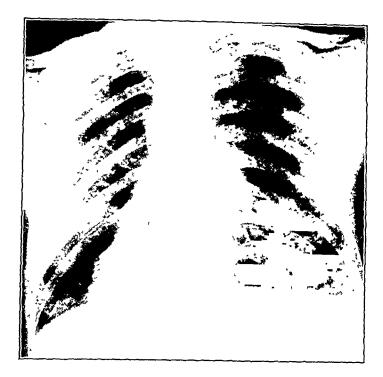


Fig. 3. Diffuse, severe, Brucella bronchopneumonia in Italian veteran; profuse, thin, muco-purulent sputum; slow, complete resolution.

seen at the Naval Hospital, illustrate the diagnostic value of radiography in brucellosis and the fact that brucellosis must be kept in mind whenever atypical findings are encountered. Brucella pneumonia is not of rare occurrence. Beatty has reported many cases. The organism was isolated from the sputum in two cases by Eyre. Lobar pneumonia due to Brucella often presents a radiographic picture similar to that shown in Figure 2, with a fan-shaped area of consolidation radiating from the hilum toward the periphery. The bronchopneumonic process shown in Figure 3 is not typical of Brucella bronchopneumonia but is, I believe, unique in its severity and diffuse distribution. Obviously this radiographic picture suggests miliary tuberculosis or miliary carcinomatosis as much as it does bronchopneumonia. Resolution was very slow, sputum thin and extremely profuse (averaging two large sputum cupfuls per day). There was ultimate clearing and recovery. There was no evidence of bronchiectasis. The first patient was Maltese, the other Italian. The Maltese sailor had lived in Malta and had brucellosis in childhood.





Fig. 4

Fig. 5

Fig. 1 Hypertrophic arthritis and degenerative bony changes in brucellosis; good functional response to Brucella abortus vaccine.
Fig. 5 Brucella spondylitis; same patient as shown in Fig. 4.

Arthritis: Brucella infection must be considered in the differential diagnosis of arthritis. The infection has been shown to be a direct or indirect causative factor in some cases of all types of arthritis. Brucellosis should be routinely considered and careful diagnostic study made in all cases unless other cause has been demonstrated and successful therapy instituted. In communities where raw milk has been in general use an amazingly high percentage of the run-of-the-mill cases of arthritis have been found associated with brucellosis and responding to specific therapy of Brucella infection. By this I do not mean shock therapy. In one such community Goldfain reported an incidence of 50 per cent. The incidence is lower in urban communities. While it has never been accurately estimated, my own experience has shown that it is by no means negligible. Differentiation is difficult. Clinically there is little to distinguish Brucella arthritis from arthritis of other origin. As in other forms of brucellosis the condition is likely to be atypical to some degree. which should be the cue for thinking of Brucella infection. Any joint may be involved but quite often the involvement is bizarre, involving



Fig. 6. Arthritis of shoulder and degenerative changes in head of humerus in woman of 68; complete functional recovery following Brucella abortus vaccine.

the metatarso-phalangeal joint of the great toe, as in gout, or the metacarpo-phalangeal joint of the thumb or several small joints limited to the medial or lateral half of one hand or foot. When involving knees, wrists or hips there is likely to be no clinical suspicion that one is not dealing with the usual types of atrophic or hypertrophic arthritis. Under all circumstances the differential diagnosis depends upon laboratory evidence that the patient has active Brucella infection and on response of the arthritic process to specific therapy. Obviously an unrelated arthritis may exist in patients with brucellosis. Therapeutic test doses of vaccine, if followed by improvement in the joint condition, with commensurate rise in the phagocytic index, furnish the best criterion in the absence of positive culture. Culture is most likely to be positive in intermittent hydrarthrosis and other acute or chronic joint effusions, especially of melitensis origin.

Figures 4 to 7 illustrate radiographic changes in these cases. You will see some changes, notably atrophic areas in bone, that are not usual in arthritis of other origin. All had positive tests for, and clinical symptoms of, brucellosis and all responded to treatment with Brucella abortus vaccine, without shock-producing reactions. Periarthritis of the shoulder joint is not infrequently encountered. It seems most likely to follow mild trauma in patients with latent or active chronic brucellosis.

Rheumatic Fever: In the acute joint manifestations resembling rheu-



Fig. 7. Hips and pelvis of same patient shown in Fig. 6, five years later; clinical recovery from arthritis of hips followed resumption of specific vaccine.

matic fever seen in patients with brucellosis the problem may be simplified by finding low or normal sedimentation rates, positive tests for brucellosis and clinical response to Brucella vaccine, with serologic confirmation of the response, or response to one of the sulfonamides. When the sedimentation rate is high, as it may be in some acute joint manifestations of brucellosis, and especially when the tests for brucellosis are equivocal, the distinction from rheumatic fever is more difficult. Of course, the patient with chronic brucellosis may also develop true rheumatic fever. When, in addition, there is a mitral valve lesion with evidence of endocarditis, the differential diagnosis between brucellosis and rheumatic fever is impossible unless blood culture is positive for Brucella or for streptococci. Positive blood culture during life and the finding of vegetative endocarditis at autopsy, with positive Brucella cultures from the endocardial lesions, have been reported repeatedly. In the absence of complicating subacute bacterial endocarditis with positive blood culture there are, of course, no definitive tests for rheumatic fever.

Ostcomyelitis: Figures 8 to 10 show extensive Brucella ostcomyelitis in one patient. I will take only time enough to point out that this young woman suffered from exacerbations of a spreading ostcomye-



Fig 8, 9 and 10 Brucella osteomyelitis of femure in young woman, onset 1924 at age 11. Regression following institution of vaccine therapy in 1935; clinical recovery. Fig 8 in 1930; Fig. 9 in 1935; Fig 10 in 1940

Fig. 8

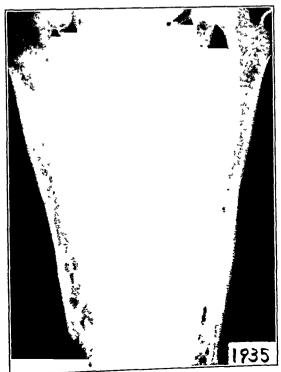






Fig 10

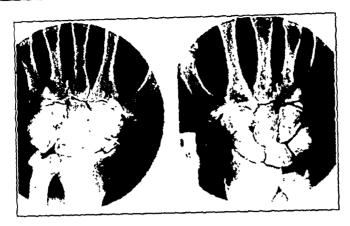


Fig. 11. Degenerative changes in carpal bones of right hand following slight trauma. Partial response to treatment with vaccine following establishment of diagnosis one year later.

litis of both femurs from 1924 until 1935 before the nature of the infection dawned upon me while studying a peculiar illness from which she was then suffering. That acute illness resolved itself into an atypical salpingitis accompanying general manifestations of brucellosis. In the eleven years between 1924 and 1935 she had had three operations on the femurs. On looking back over the reports it was found that organisms having typical morphologic and cultural characteristics of Brucella had been recovered at two of the operations (1924 and 1929) but had not been recognized because the behavior of Brucella abortus was not then widely known. The improvement shown since vaccine therapy was begun in 1935 is evident. She is now quite well clinically, is married and has had a child. However, whenever vaccine is discontinued for more than a few weeks there are evidences of clinical and serological relapse.

Neurosis: Neurosis is probably the most frequent erroneous diagnosis made in chronic, afebrile brucellosis or in patients with low-grade fever and complaints of fatigue, weight loss, joint and muscle pains, headache, mental confusion, backache, and the like. These patients may go the rounds of physicians and cultists over a period of years before someone recognizes the syndrome and carries out the tests, or stumbles upon the diagnosis through routine use of the tests. Often attention is called to the correct diagnosis only if the patient develops obvious objective symptoms or an acute febrile illness. Admittedly the differential diagnosis is difficult for brucellosis may produce a perfect textbook picture of neurosis, as pointed out by Evans after bitter personal experi-



Fig. 12. Peri-arthritis and bursitis of shoulder following slight strain; exquisitely tender and painful for six months before vaccine therapy; complete recovery in four weeks.

ence. Errors in both directions are bound to occur but they can be kept to a minimum by careful study.

Involvement of Central Nervous System: Neurobrucellosis is perhaps a good term for involvement of the central nervous system, which is not nearly as rare as is generally believed. Many reports have reached the literature but the diagnostic evidence is often meager unless Brucella can be recovered from blood or spinal fluid or from tissues at autopsy. The death rate in brucellosis is low; therefore autopsy material is not plentiful. The pathologic findings may not be helpful in differential diagnosis. While there is no characteristic picture that may be entirely relied upon, there is a growing literature tending to show that the histopathology of Brucella involvement of the brain and its coverings, while often resembling tuberculosis, especially in its tendency to nodule formation, is at least suggestive. Such a case was under my observation on my wards at the Brooklyn Naval Hospital more than a year ago. An enlisted man of twenty-four had such vague complaints of fatigue, epigastric discomfort and other symptoms suggesting ulcer, frequency and burning of urination, leg pains and cough, as to lead various medical officers to ascribe all of his symptoms to neurosis, since physical examination was essentially negative. Recurrent attacks of iritis

constituted the only objective finding, occurring several times yearly for the previous five years according to his history. Tests were positive for brucellosis but he failed to respond in the usual favorable way to Brucella vaccine. Artificial fever therapy was being considered but events subsequent to Pearl Harbor resulted in my transfer and in his survey out of the service, with a diagnosis of brucellosis. His subsequent history was given me by members of the staff of the University of Kansas Hospital. Within a month of his return to civilian life he had begun complaining of severe headaches and nuchal stiffness, usually of short duration. Then had followed, within a few days, an attack of sharp pain in the left frontal region and, four days later, weakness of the right leg and a tendency to limp. Ten days later he had had a sudden right sided hemiplegia which failed to clear up. Aside from the hemiplegia, findings were indefinite, with a questionable degree of choking of the left optic disk, moderate increase of deep tendon reflexes on the right, positive Babinski and ankle clonus, spinal fluid pressure of 280 mm., clear spinal fluid, and a cell count of 33, mainly lymphocytes. Three weeks following the onset of the hemiplegia a burr hole was made and a ventricular cannula passed toward the left lateral ventricle. Biopsy material consisted of a reddish brown, soft, cellular, granular tissue grossly resembling rapidly malignant tumor tissue or encephalitis from a recent subcortical hemorrhage. He died the same day of respiratory paralysis. At autopsy the cerebrum showed rather poorly defined areas of softening and disintegration of the brain substance. Sections through the region of the left internal capsule showed extensive acute and chronic inflammatory reaction with wellmarked cuff-like accumulations of monocytes and polymorphonuclear leukocytes in the perivascular spaces. Numerous large phagocytic mononuclear cells containing congested polymorphonuclear leukocytes were recognized in many areas. Polynuclear leukocytes were diffusely scattered through the nerve tissue in some sections. There was considerable spongy degeneration and softening in the nerve tissue associated with edema, and in some areas considerable hemorrhage. Numerous compound granular corpuscles were seen in some fields and many Nissl plump cells. The diagnosis was encephalitic encephalomalacia complicating chronic brucellosis. Unfortunately no attempt was made to re-

DeJong and others have reported instances of central nervous sys-

tem involvement in which the diagnosis was confirmed by culture and in which there was similar histopathology.

A patient with post-encephalitic Parkinsonian syndrome, apparently due to brucellosis, had been ill for nine years with a progressive, constant gross tremor of the right arm and leg and marked swelling of the entire right upper extremity of a disabling degree. Improvement was so marked following vaccine therapy as to allow her to resume her household duties.

Illustrative Case History: The following case history illustrates a differential diagnostic problem frequently encountered: A housewife of twenty-eight complained chiefly of fatigue and loss of weight. She had been ill for nearly a year following a vague febrile illness of two weeks duration which had been diagnosed as grippe. A productive cough had continued since. She also complained of frequent attacks of right lower quadrant pain. She had been operated on three months previously and a normal appendix removed. Enlargement of regional mesenteric glands had been noted (a common finding in abdominal manifestations of brucellosis). Weight loss had aggregated 18 pounds. There had been occasional periods when she felt quite well and regained a little weight. Various joints had been involved in a subacute arthritic process, with periods of complete remission.

After study at an excellent hospital no diagnosis other than "arthritis" was made. Physical examination, all usual routine laboratory examinations, including chest and gastrointestinal x-ray, had been essentially negative. Repeated sputum examinations had been negative for tubercle bacilli. There had been noted a moderate secondary anemia of the macrocytic, hyperchromic type, with normal total white count and moderate increase in lymphocytes. There had been occasional fever of from 99.2 to 99.6 degrees. The right tube had been barely palpable and moderately tender on one occasion.

Brucellosis had not been considered nor the tests done. The multiple tests for brucellosis, tuberculin test, blood complement test for tuberculosis and culture of blood and urine for Brucella were then undertaken and the sedimentation rate redetermined. Blood agglutination test was negative, skin test with Brucella organisms was positive, the phagocytic index was low (0-0-9-16), sedimentation rates were within normal limits, blood and urine cultures were negative, blood complement test for tuberculosis showed an insignificantly low titer, and tuberculin test

was positive. There was, then, an array of positive and negative laboratory findings, none of which were definite enough to diagnose or rule out tuberculosis, brucellosis or an atypical rheumatic fever. The normal sedimentation rates furnished strong evidence against tuberculosis or rheumatic fever, however. The remaining reports were not without significance when viewed in the light of the suggestive history and the lack of definite physical findings to account for it. The positive skin test for Brucella sensitization, coupled with the low phagocytic index, the normal sedimentation rate and normal white count with relative lymphocytosis, together with the history, led to a tentative diagnosis of chronic brucellosis as the possible explanation of all her complaints.

A further clue lay in the fact that many of her previous symptoms had recurred during the skin test reaction and had then subsided. Therapeutic test doses of specific vaccine furnished the last link in the chain of evidence. The first dose was followed by a mild local, focal and general reaction; the arm was tender, slightly swollen at the site of the injection, the right wrist and left knee joints became lame and moderately swollen, pelvic pain was aggravated, the right fallopian tube was tender and palpable, malaise and fatigue were increased, temperature was elevated to 100.2 degrees, within 24 hours. On the third day, following, all signs and symptoms accompanying the exacerbation ascribable to the vaccine reaction had subsided and the patient reported feeling definitely better. Following three subsequent doses of vaccine, attended by no reactions, marked subjective and objective improvement was apparent. The phagocytic index rose sharply, 10 cells now showing marked phagocytosis, 9 moderate, 6 slight and 0 none, as compared with 0-0-9-16 prior to treatment. Within three months, under continued treatment, the patient seemed well and the phagocytic index was at a still higher level (19-5-1-0). The patient was instructed to return for check-up and repetition of the phagocytic index at monthly and then longer intervals. She failed to appear until four months later when her index was found at a lower level (5-5-7-8), suggesting the likelihood of impending relapse. Resumption of vaccine was advised but the patient asked permission to defer it because she felt well, but largely because her brother-in-law, a capable internist, had expressed the doubt that she ever had had brucellosis, ascribing her recovery to coincidence or to non-specific action of the foreign protein injections. Six weeks later the patient returned saying that most of her old symptoms had recurred and that she would now be coöperative. The phagocytic index was very low (o-8-10-7). Response to vaccine was rapid. She was treated for four months during which time she remained well. The index rose to 21-4-0-0 and remained at a high level for the next three years, without treatment. She then developed a severe measles, following which she failed to convalesce completely, complaining of great fatigue, joint lameness and malaise. She deferred returning for further observation as she was assured that this syndrome could not also be a part of an uncured brucellosis. When she did appear several months later her index again was found to be at a low level, as so often is observed in brucellosis following depleting illnesses. She was given six doses of vaccine and has remained well for the past two and a half years.

Grippe, influenza, typhoid fever, malaria, acute abdominal conditions, atypical meningococcic cerebrospinal fever can only be mentioned as among the many other illnesses that have to be considered in the differential diagnosis of acute brucellosis. Chronic brucellosis must be differentiated from endocrine dysfunctions, neuritis of other origin and a host of other diseases and syndromes in addition to the few discussed above.

Splenomegaly is not a differential diagnostic finding of value. It is mentioned because it has been said to be pathognomonic of brucellosis. It is present in a small percentage of cases of chronic brucellosis and in a higher but variable percentage of acute infections, especially of melitensis origin.

TREATMENT

Treatment must be outlined rather than discussed in detail. No one method can be relied upon in all cases. Many of the methods widely discussed in the literature, particularly intravenous typhoid vaccine, have proved to be valueless in my experience and that of others.

Specific Vaccine Therapy: For treatment of chronic brucellosis, heat-killed Brucella abortus vaccine has given the best results in my hands, and, with various modifications, in the hands of others who have treated significant numbers of patients and have observed them for adequate periods of time. Foshay and O'Neil have had splendid results from a nitrous acid treated Brucella vaccine which can be used without undue reaction even in the acute illness. Huddleson's Brucellin, a filtrate of all three strains of Brucella, has had favorable reports, especially in

the treatment of recent cases, but its use is attended by deliberately induced severe reactions. Many of the favorable reports of its use have not covered sufficient periods of time to allow of its proper evaluation. The commercial vaccines made from mixed strains of Brucella are best avoided because of the greater reactions induced by the presence of melitensis or suis strains. The abortus strain produces maximal immunologic response in the presence of infection due to any of the three strains. Calder believes that the presence of the suis or melitensis strains in vaccine is likely to lessen rather than to increase resistance.

The method of use of vaccine is of paramount importance. Reactions are best avoided in the majority of patients. It is not the foreign protein or shock effect upon which the efficacy of Brucella vaccine therapy rests. Dilutions of 1:10, 1:100 and 1:1000 are used to initiate treatment in sensitive patients. Intravenous vaccine is usually efficacious in those who are refractory to the intramuscular route, especially when sensitivity to vaccine persists in spite of carefully graduated dosage. Each patient's treatment must be individualized. As with other methods in other illnesses, much of the unfavorable viewpoint toward specific vaccine therapy of brucellosis comes from the experience (or inexperience) of those who have used an ineffective vaccine or ill-advised dosage, or in poorly selected cases.

Fever Therapy: When vaccine therapy fails to bring about recovery, after thorough trial and adaptation to the patient, as it will in perhaps 10 per cent of cases, other methods may be effective. Artificial fever therapy is believed by many careful observers to be the method of choice in cases refractory to vaccine therapy. It is essential to select patients carefully, to know their possible idiosyncrasies to pre-treatment sedatives and opiates and also to know their psychologic reactions to fear-producing situations. Some patients cannot help but think of the treatment cabinet as a coffin and to react badly. The optimum fever level seems to be from 105 to 106 degrees for five hours for from three to six treatments. Good results in Brucella spondylitis and other manifestations of brucellosis are reported from the Mayo Clinic and elsewhere.

Sulfonamides: The sulfonamides are of value in terminating the acute illness but not uniformly so, nor are the patients necessarily cured. Relapse follows in a variable percentage. Clinical evidence of the value of all the sulfonamides, including sulfaguanidine, has been presented by many but in no large nor controlled series. In the chronic illness they

seem to be of less value but undoubtedly sometimes are efficacious, apparently supplementing the effect of vaccine or fever therapy. Horn has reported good results from small doses over long periods of time, along with or alternating with vaccine. My own results in chronic brucellosis have not been consistent. In the subacute joint manifestations neoprontosil (oral) gave splendid results in two patients. Naturally one hopes that a compound will be synthesized that will have more uniformly specific bacteriostatic effect in the presence of all Brucella infections.

Serum and Other Methods: Foshay's serum, of goat or horse origin, has given excellent results in bringing about prompt remission in acute cases of less than four months duration. Relapse must be watched for in these patients, however. Transfusions of immune blood also have been favorably reported on in tiding patients over the acute illness.

The value of intravenous arsenicals such as neoarsphenamine is open to question. Wainwright is enthusiastic about it, as was Forest, but until recently it was uniformly unsuccessful in all of the various manifestations of brucellosis in which I employed it. Among them were two patients under treatment for syphilis, also suffering from brucellosis. They had the usual courses of neoarsphenamine and bismuth but showed no improvement in the co-existing Brucella infection until, months later, vaccine was also employed. However, one patient with a history of long-standing choroiditis, presumably a part of her Brucella infection, failed to improve under vaccine or artificial fever therapy but did respond surprisingly well to intravenous mapharsen.

In evaluating results of treatment it must be remembered that there is no absolute criterion of cure. Maintenance of a high level of phagocytic activity for many years is of utmost importance. Results must be couched in terms of "recovery," or at most, "apparent cure." The illness is prone to relapse, spontaneously or after intercurrent illness over an indefinite number of years unless carefully guarded against. It is by no means a self-limiting illness as so many of the standard texts still state; no more than is tuberculosis.

In concluding I would like to thank you for bearing with me in this rambling and incomplete discourse, and to take the opportunity to reëmphasize several points:

1. The diagnosis of brucellosis depends upon the intelligent use of the four recognized laboratory methods, with correlation of them with

the clinical findings.

2. Negative tests, individually or in aggregate, may not be relied upon to rule out brucellosis. Positive culture has been found in the presence of negative agglutination test and negative skin test and regardless of the opsonic index.

3. Positive tests must be evaluated carefully, except for positive culture which is definitive. A positive skin test alone is not proof of the

existence of active brucellosis.

- 4. When properly arrived at, the diagnosis of brucellosis rests on firmer ground than that of many other illnesses, notably rheumatic fever.
- 5. The first essential to diagnosis is the willingness of the physician to admit the possible existence of brucellosis.
- 6. The diagnosis of brucellosis must be considered in all obscure illnesses, acute or chronic.
- 7. The differential diagnosis must include differentiation from innumerable diseases and syndromes ordinarily not thought of as simulated by brucellosis.
- 8. Known methods of treatment are satisfactory in a large percentage of cases.

CLINICAL RESEARCH ABSTRACTS*

Studies on the Etiology of the Renal Shutdown Following Crush Injuries**

R. J. Bing

Bywaters has indicated that renal failure following crushing injuries may be caused by the excretion of metmyoglobin in the presence of acidosis. The present study deals with the effect of metmyoglobin on the renal function of the acidified dog and with a comparison of its action with that of hemoglobin and methemoglobin in the normal and acidotic unanesthetized animal. Creatinine or mannitol clearances were used to measure glomerular filtration rate, paraminohippuric acid clearances for the determination of the effective renal plasma flow. Glucose Tm was determined in order to obtain information on the reabsorptive tubular capacity. Acidosis was produced by oral administration of from 80 to 100 gr. of ammonium chloride.

The infusion of metmyoglobin in five instances or of crystalline hemoglobin and hemolyzed blood in seven cases had no effect on the renal clearances of the acidotic animal. Hemoglobin infusions into three normal animals were equally ineffective. The infusion of from 4 to 12 gr. of crystalline methemoglobin into 12 acidotic dogs produced a progressive fall in clearances and in the urine flow and an increase in the blood urea during the four days following the infusion. The renal lesions consisted of hydropic tubular degeneration and necrosis, accompanied in some instances by cast formation. Methemoglobin infusions into animals with normal alkali reserve or oral administration of ammonium chloride alone resulted in no change of renal function.

The Relationship Between Blood Concentration and Blood Volume in Cardiac Decompensation

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Evidence of a conclusive nature has been presented by Gibson and Evans¹ that recovery from cardiac decompensation is always attended by a fall in blood volume as measured by a dye method (Evans blue). On the other hand, Stewart² has shown that during the period of recovery from cardiac decompensation there is a fall in the specific gravity of the plasma. Since it is now generally accepted that a fall in specific gravity of the plasma indicates hemodilu-

tion (or vice versa) the results of these two groups of investigations would appear to be divergent. This paper is an attempt to elucidate this problem by measuring both blood volume and plasma specific gravity in the same patient during the recovery period from decompensation.

The results obtained in a group of 24 cardiacs show that when recovery from decompensation is prompt, as evidenced by falling venous pressures and diminished cir-

^{*} These are abstracts of presentations before the Clinical Research meeting held May 27, 1943, at The New York Academy of Medicine. This meeting was arranged by the Committee on Medical Education of the Academy.

^{**} From the Department of Physiology, New York University, College of Medicine, aided by a grant from the Josiah Macy Jr. Foundation.

culation times, there is not only a fall in total blood volume but also a fall in plasma specific gravity. This fall in specific gravity of the plasma occurs only during the first portion of the recovery period and later returns to control values. There is also a fall in hematocrit values during this period. In cardiacs who recover very slowly from decompensation or in whom there is little diminution in blood volume these changes in blood concentration were not noted.

No explanation is apparent in this investigation for the paradoxical hemodilution of the blood during a period when the blood

volume is actually diminishing. However, the results portray the advantageous physiological mechanism which exists in those cardiacs who do recover from decompensation. For during the period of recovery not only is there less blood to circulate, but it is also lighter in weight. Moreover, these findings suggest that more caution be used in interpreting blood specific gravity changes in conditions where rapid circulatory adjustments take place, as for example the shock syndrome.

Gibson, J. G. and Evans, W. A. S. J. Clin. Investigation, 1937, 16:833.
Stewart, H. S. J. Clin. Investigation, 1941, 20:1.

* * *

A New Method for the Subcutaneous Administration of Heparin

LEO LOEWE and PHILIP ROSENBLATT

From the Department of Laboratories, Jewish Hospital, Brooklyn, New York

In reporting on a new method of administering heparin originally devised for animals, 1.2 it was stated that the method was being adapted for humans. With the cooperation of the Roche-Organon Company, a menstruum was developed for effecting slow and equable heparinization by the subcutaneous route.

This method was applied to humans with gratifying results. It has made possible and practicable the use of safe anticoagulant therapy over protracted periods. Nine cases of phlebothrombosis and thrombophlebitis and one case of subacute bacterial endocarditis have been satisfactorily treated for as long as two to seven weeks. Continuous heparinization by the cumbersome venoclysis method for more than two weeks is vir-

tually impossible of accomplishment. The more extensive use of heparin should be encouraged by the development of this simple, effective, and more economical means for its administration.

It is important that heparin be made more available at the present time because of its application in war surgery, in the field of blood vessel surgery, and for the prevention of postoperative thrombosis and embolization. It is felt that this method of depositing heparin subcutaneously, or some further modification of it, will encourage the more widespread and rational use of this valuable anticoagulant.

* * *

Modification in Surgical Treatment of Herniated Nucleus Pulposus

LEO M. DAVIDOFF

In view of the desirability of producing fusion of the spine after the removal of herniated disc in many cases, a simple method for carrying out fusion has been devised, utilizing the spinous process of one of the vertebrae which is fashioned into a wedge, shaped like a double clothespin and

inserted between the stumps of the spinous processes of the vertebra above and below the space where the disc occurs. In addition to the wedge, fragmented pieces of the other spinous process are used to fill the remainder of the space.

Loewe, L., Rosenblatt, P. and Lederer, M. Proc. Soc. Exper. Biol. & Med., 1942, 50:53.
Loewe, L. and Rosenblatt, P. Am. J. Path., in press.

The Concentration of Vitamin A in the Blood Plasma During Pregnancy

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Plasma vitamin A and carotene determinations were carried out in 120 women at various stages of pregnancy. In twelve of these, the blood plasma was analyzed some time during the first two trimesters and again in the ninth month. The subjects were advised to eat their usual diet and a record of their dietary intake, especially with regard to vitamin A-containing foods was kept. No carotene or vitamin A concentrates were added to the diet.

The results of this study indicated that the level of vitamin A in the plasma decreases during the third trimester of pregnancy. Thus, the mean value of the vitamin A concentration in 70 women who were 6 months pregnant or less was 105.4 international units per 100 cc. of plasma (standard deviation 23.2) whereas the mean value of the determination for the 62 women in the last trimester was 91.1 international units of vitamin A (standard deviation 26.2). The difference between the mean value for the first trimesters 105.4 I.U., and that for the third trimester, 91.1 I.U., is 14.3 I.U., which is more than 3 times the standard error of the difference between the two means and hence is statistically

significant.

That the level of vitamin A in the plasma decreases during pregnancy is also evident from a study of individual subjects. The plasma concentration of vitamin A was determined sometime during the first 6 months of pregnancy and again during the ninth month in each of 12 subjects. Nine of these women exhibited a drop in the plasma vitamin A concentration during pregnancy, the decreases ranging from 8 to 88 international units and averaging 37 international units. The concentration of carotene in the blood plasma does not fall during pregnancy. This may be due to the fact that only small amounts of carotene pass from the maternal to the fetal circulation.

The decrease in plasma vitamin A during the last three months of pregnancy is probably due to storage in the fetal liver as well as to utilization of vitamin A by the fetal tissues. Studies are now in progress to determine whether the addition of a vitamin A concentrate to the diet of pregnant women will prevent a fall in the vitamin A blood levels during the last three months of pregnancy.

Acute Infectious Lymphocytosis*

CARL H. SMITH

In 1941, I reported two cases of acute infectious lymphocytosis¹ in young children who, with a minimum of clinical signs and symptoms, showed an unexpected and exaggerated lymphocytosis with maximum leukocyte counts of 44,300 and 98,000 per c. mm., respectively. During March, 1943, within a period of 3 weeks, several cases of the same condition were observed at the New York Hospital. Studies made among the members of this group lend further support to the view expressed previously¹ that

this condition is a specific entity possessing infectious and communicable aspects.

A child, M.S., 5 years of age, was admitted to the hospital on March 3, 1943, because of abdominal pain. The blood count showed 55,400 white cells per c. mm. with 72 per cent lymphocytes. On March 15, two other children in this family, and on March 22, K. C., a hospital contact, showed a similar blood picture. In all of the affected children the leukocytosis and lymphocytosis persisted for approximately 3 weeks. The lym-

phocytes were of the normal, small, and intermediate variety. The heterophile test was negative in the four patients. Sternal aspiration in M.S. and K.C. showed an increased lymphocytic percentage. The course in each was benign and the spleen and lymph nodes were not enlarged. A lymph node was removed for biopsy from M.S. and from K.C., and in each a strikingly similar picture was noted, consisting of obliteration of the lymph follicles with marked proliferation of the reticuloendothelium of the sinuses. Serological studies

for lymphocytic choriomeningitis, influenza A and B, were negative.

Acute infectious lymphocytosis can be differentiated clinically, hematologically, and serologically from infectious mononucleosis, leukemia, and miscellaneous infections associated with lymphocytosis. It probably represents a heretofore unrecognized communicable disease in which the blood picture serves as an expression of the infection.

Neuro-Hormonal Regulation of Water Balance: Studies in Patients with Diabetes Insipidus

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New York Medical College, Flower and Fifth Avenue Hospitals

Water, sodium, and chloride balances were studied in four patients with proved diabetes insipidus under a variety of standardized conditions.

The primary role of the polyuria of diabetes insipidus was demonstrated by water restriction and salt loading tests. The total urinary output was decreased or increased at will by the administration of diets low or high in salt, respectively. Inulin clearance revealed a normal type of variation in glomerular filtration in response to varying amounts and concentrations of salt. Improved elimination of salt and contraction of urinary volume to normal was readily accomplished by the use of posterior pituitary extracts.

Alpha-estradiol dipropionate in 10 mg. doses daily produced a positive chloride bal-

ance equivalent to as much as 3.5 gm. of sodium chloride daily in one instance, with a concomitant contraction of urinary volume, no appreciable change in specific gravity or concentration of chloride in the urine, and a normal glomerular filtration.

Desoxycorticosterone acetate in 10 and 20 mg. doses daily for five days caused at first a marked retention of sodium with decreased urinary volume and chloride concentration. In the "release" phase a negative sodium balance and an increased urinary output and concentration of chloride resulted.

Amidopyrine decreased the polyuria with a simultaneous increase in the urinary specific gravity and concentration of chloride. No effort was made to determine the nature of this effect.

Test of Viability of the Gut in Local Obstructions

JOHN HERRLIN and S. T. GLASSER

The problem of determining the viability of intestine not infrequently presents itself in cases of obstruction. In these instances,

surgical judgment implies a difficult decision even in the best of hands. One must choose between a simple release of the obstruction,

^{*} From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

¹ Smith, C. H. Am. J. Dis. Child., 1941, 42:231.

and resection with anastomosis. The mortality in the latter is obviously increased. Since the pathology observed is usually dependent upon vascular changes, we are confronted with a situation analogous to one seen in cases of peripheral vascular disease, namely, reflex or axone—reflex spasm of the collateral circulation. We have based our test which is also of therapeutic value, on this principle. A perivascular injection of

novocain into the mesentery of the involved segment often results in a prompt restitution (one to two minutes) of the intestine. In some instances the novocain injection placed at the mesenteric border of the gut proves more satisfactory. Further experiments are being conducted at the New York Medical College towards a better understanding of the mechanism involved.

A New Experimental Laboratory Animal, the South African Clawed Frog (Xenopus laevis): Its Use in Pregnancy Diagnosis, Hormone Assays, and Endocrine Evaluations

ABNER I. WEISMAN and CHRISTOPHER W. COATES

Jewish Memorial Hospital and New York Zoological Society

Xenopus laevis Daudin, the South African clawed frog, is established as a new, satisfactory, and versatile laboratory animal. The use of the animal is predicated on the response—extrusion of eggs—to hormone stimulation. Its chief present value is its remarkable accuracy in the early diagnosis of pregnancy; the speed with which the diagnosis may be made, and the ease with which the diagnosis may be read; 641 cases are reported with 99 per cent accuracy. No false positives are recorded. Reports on gonadotropic hormone assays indicate that

true anterior pituitary extracts are more potent than either of the gonadotropes obtained from pregnancy urine or serum.

Tubal pregnancy diagnosis was confirmed in 9 cases.

In clinical endocrinology, neither climacteric nor post-climacteric urines gave positive results, but urine from cases of hydatid mole gives positive results in extremely small dosages.

Further studies are being made in glandular neoplasms.

The Complement-Fixation Test for Lymphogranuloma Venereum: Results Obtained With Its Use

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A number of complement fixation tests for lymphogranuloma venereum were uncertain and unsatisfactory owing to the low concentration of virus in the antigens. The growth of the virus in the yolk sac of the developing chick has enabled suspensions of the virus to be obtained which are practically free from inert material. Antigens of any desired concentration of virus can,

therefore, be prepared which are both sensitive and specific. By their use it has been shown that about 50 per cent of persons with gonorrhea or acquired syphilis have, in addition, asymptomatic lymphogranuloma venereum. Examination of the sera of children with congenital syphilis has proved that there is no cross fixation between the reagins of syphilis and those of lympho-

granuloma venereum. Agreement between the results obtained with the Frei intradermal test and the complement fixation test has been found in 85 per cent of a group of 200 normal and lymphogranulomatous people. The bulk of the remaining persons had a positive complement fixation reaction and either showed clinical manifestations which could be regarded as lymphogranulomatous or had other venereal diseases. It is, accordingly, felt that the complement fixation test is a more sensitive procedure for the diag-

nosis of lymphogranuloma venereum than is the Frei cutaneous test. There is a definite relation between the average size of the Frei reaction and the average level of the complement fixing titre of the sera of lymphogranulomatous persons; the larger the reaction, the higher the titre. It was also found that the average titre of sera of cases of proctitis with stricture was 6 to 7 times greater than that of persons in whom the lymphogranulomatous infection was, and had always been, asymptomatic.

The Role of the Lymphatics In Ascending Urinary Infections JOHN L. ALLEY*

A discussion of the anatomy of the lymphatic system of the genitals in its relationship to the urinary apparatus. The possibility of extension of infection to the kidney from below is admitted, but the precise route is subject to controversy. Efforts were made to inject the lymphatics in rabbits and guinea pigs with India ink. The ink was sterilized, diluted with an equal amount of normal saline, and injections were made into the corpora of the penis. Multiple injections at varying intervals were made. Careful examination of the tissues of autopsied pigs were then made and sketches accompany the presentation.

Conclusions: Infections apparently may spread upward in the genito-urinary system. The burden of drainage from the lower organs is borne by the lumbar lymphatics. On reaching the level of the kidneys, infection may go on past to empty into the blood stream and thence to the kidney, or it may reverse the normal lymphatic flow at this level to invade the kidney by way of the perivascular lymphatics.

Certain New Considerations In Local Sulfonamide Therapy*

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Controlled observations have shown that the local use of sulfonamides has not scored the brilliant results that follow their use in systemic infections. It is the purpose of this paper to describe the results of studies of infected wounds in man that have revealed certain heretofore unrecognized factors that may lead the way to successful local sulfonamide therapy of infected wounds.

From the experimental observations as shown in charts, diagrams, and in color photographs these new considerations of local sulfonamide therapy may be summarized:

- (1) Present techniques of application maintain but slight if any concentration of drug in the infected wound. Absence of drug coincides with failure to control infection,
 - (2) Infected wounds develop very low

^{*} Graduate Fellow in Surgery, New York Medical College, Flower and Fifth Avenue Hospitals; under the direction of Joseph H. Fobes, Department of Graduate Surgery, New York Medical College, and Professor J. A. Hyams, Post-Graduate Hospital.

hydrogen ion concentrations: pH of 5.0 to 55 is frequently measured in the exudates.

- (3) The lowered hydrogen ion concentration reduces the activity of sulfanilamide 10 to 100 times so that practically unattainable concentrations are required for bacteriostasis in the acidic exudates.
- (4) Sulfadiazine and sulfathiazole (which are many times more potent than sulfanilamide) are not greatly "inactivated" by the lowered pH but they are rendered insoluble. This prevents their dissolving in wound fluids and exudates, a prerequisite for control of infection. Use of their highly soluble

sodium salts overcomes this major obstacle and produces bacteriostasis without irritation to tissues or delay in the growth of epithelium.

(5) Persistent failure to detect sulfonamide "inhibitors" in numerous samples of pus (obtained without novocaine) suggests that failures with local sulfonamide therapy may be the result of the four previous factors and not because of the presence of various types of "inhibitors."

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Nutritional Deficiency In the Etiology of Menorrhagia, Metrorrhagia, Cystic Mastitis and Premenstrual Tension: Treatment With Vitamin B Complex

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In previous experiments in the rat, it has been found that the liver loses its ability to inactivate estrogen in vitamin B complex deficiency and that this function can be restored by the addition of brewers' yeast to the diet. In contrast, the inactivation of androgen was found not to be significantly impaired in vitamin B deficiency. Failure to inactivate estrogen while androgen continues to be inactivated leads to a serious alteration in the estrogen-androgen equilibrium. On the basis of these animal experiments an investigation was made to determine whether there is any clinical

correlation between nutritional deficiency and the occurrence of syndromes related to an excess of estrogen, in particular, menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension. A striking correlation was found and therapy of these conditions with vitamin B complex was therefore attempted. Prompt and often dramatic improvement occurred with vitamin B complex orally or orally and parenterally. Oral lesions of nutritional deficiency in patients with the syndromes associated with an excess of estrogen, and the changes under treatment, are illustrated in Kodachrome.

^{*} This work was done under a contract between the Office of Scientific Research and Development and Columbia University.

Titration and Neutralization of the Western Strain of Equine Encephalomyelitis Virus In Tissue Culture

C. H. HUANG

From the Departments of Medicine and Bacteriology, College of Physicians and Surgeons Columbia University

Instead of injecting the virus or serumvirus mixtures into animals, one drop of the material from each dilution was inoculated into tissue cultures. After 48 hours of incubation, pieces of tissue from each culture were transferred and patched with plasma in Carrel dishes. They were incubated and readings were made under low power microscope 48 hours later.

It was found that cells which were not infected or had overcome the infection, grew out in the plasma patch. Contrariwise, when virus was present, no growth from the explant was observed.

The method hereby presented has several advantages, namely: reduction of cost of

experiments since one chick embryo can be used for a complete titration experiment; removal of the variable of individual animal reactivity; and the tissue culture may be a more sensitive method for the detection of the virus and neutralizing antibodies. It was found that the neutralization obtained in tissue culture is 100 to 1,000 times greater than that observed in the intracerebral mouse test.

Recently, a more simplified method has been developed with promising result. This was based on the difference in the change of the pH of the medium in infected and non-infected tissue.

The Effect of Sodium Thiosulphate on the Blood

LINN J. BOYD, LOUIS GREENWALD and JOSEPH LITWINS

Department of Medicine, Flower and Fifth Avenue Hospitals

For more than a decade this chemical has been advised for the prevention of post-operative thrombosis and other disturbances of clotting. Adequate examinations of its effect on the blood have never been conducted. In vitro and in vivo experiments have been performed by the writers on more than two hundred patients during the past year. The influence of the chemical on blood morphology, chemistry and clotting was examined. Studies were also conducted on more than one hundred patients before and after operation.

Sodium thiosulphate does influence clotting, but the solutions must be much more concentrated and the doses much larger than those employed by most clinicians. None of the untoward effects associated with heparin and dicoumarin are observed. The chemical is practically devoid of toxic effects. Observations were also made on the question of single and multiple injections.

No changes in the blood morphology occurred when enormous doses were given and the patients followed for months. There are also no significant changes in blood chemistry. There is a variable latent period before the effect appears which bears very definitely on its therapeutic application. A possible mode of action is suggested.

A Rapid Pregnancy Test (Two to Six Hours)*

U. J. SALMON, S. H. GEIST, C. S. Poole and A. A. SALMON, B.S.

The test is based on the observation that following the injection of pregnancy urine into immature female rats a vasodilatation of the ovarian vessels occurs as early as two hours after the injection. This reaction is visible to the naked eye-the ovaries being engorged, bright red in appearance and enlarged in contrast to control ovaries which are pale pink in color. In approximately 5 per cent of rats the vasodilatation is only slight at 2 hours and becomes maximal between 3 and 6 hours after the injection; 2 cc. of urine is injected under the dorsal skin of each of four immature albino rats, weight 35-45 grams. Two animals are autopsied at the end of two hours and if the results are negative or questionable the remaining two animals are autopsied four hours later. The accuracy of this reaction as a test for pregnancy was determined in a series of over seven hundred unknown specimens of urine comprising normal pregnancies, incomplete

abortions, ectopic pregnancies, hydatidiform mole, chorioepithelioma, functional amenorrhea, menopause (natural, surgical and radiotherapy), uterine fibroids, menorrhagia, metrorrhagia and functional dysmenorrhea. The accuracy of readings at 2, 4 and 6 hours were compared. Readings of the control urine specimens from normal non-pregnant women were 100 per cent accurate. Correct positive readings were made in 96.3 per cent of the pregnancy cases at 2 hours; in 97.2 per cent at 4 hours and in 98 per cent of the cases at 6 hours.

This test has the practical advantages of rapidity, simplicity of reading, inexpensiveness and ease of obtaining the test animals. The latter two are particularly important at present because of the growing scarcity and increasing cost of rabbits.

* This research was carried on at the Mount Sinai Hospital.

Nitrogen Retention, Creatinuria, and Other Effects of the Treatment of Simmonds' Disease With Methyl Testosterone

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RANDOLPH WEST

Associate Physician, Presbyterian Hospital

The use of methyl testosterone orally has produced striking clinical improvement with accompanying laboratory changes in 4 cases of marked anterior pituitary insufficiency or Simmonds' disease. The diagnosis was confirmed in one case by the complete lack of demonstrable pituitary cells at autopsy on gross and microscopic examination. Seborrhea failed to appear despite the restoration of other secondary sex characters, suggesting that androgens normally act to produce seborrhea only after the skin has been prepared by some basic mechanism or mechan-

isms, which are wanting in hypophyseal failure. From the laboratory standpoint, methyl testosterone was found to cause nitrogen retention and persistent weight gain in the absence of hypophyseal function. A marked increase in creatinuria was also noted during the period of methyl testosterone therapy.

The use of methyl testosterone is suggested as an effective therapeutic agent in anterior pituitary insufficiency or Simmonds' disease.

The Physiopathological Aspect of Muscles in Infantile Paralysis JOSEPH MOLDAVER

In this presentation an attempt has been made to discuss the chief disorders resulting from infantite paralysis. The affinity of the virus for the anterior horn cells of the spinal cord is striking. Lesions are also found in the posterior horn cells and dorsal root ganglia. In addition, other parts of the central nervous system may be affected. The paralysis is a flaccid one. The affected muscles become atrophic and toneless; the tendon reflexes and some cutaneous reflexes In the paralytic or paretic are absent, muscles, neuromuscular degeneration can be evidenced by chronaxie measurements. The degree of the injury of the anterior horn cells is evaluated by this test; the greater the lesion, the higher is the chronaxie. This helps the diagnosis and also the prognosis Muscles with total neuromuscular degeneration (completely denervated) are doomed. Muscles with partial neuromuscular degeneration (partially denervated) may recover partially or even completely. Inflammation of the sensory protoneurone is not necessarily found at exactly the same level as the injury of the anterior horn cells; therefore, pain and tenderness of the muscles may be found in non-paralyzed as well as in affected muscles. Pain is a referred pain, increased by stretching of the muscles. Clinically speaking, most of the lesions of the sensory protoneurones clear up completely; sensory disturbances are not frequently seen in the chronic stage.

A new concept was recently described by Kenny, This concept is fundamentally different from the one accepted for more than a century. According to this concept, infantile paralysis is a "spastic" not a flaccid paralysis. The muscles affected by the disease are those in so-called "spasm," "the most damaging symptom." The danger of paralysis lies mainly in allowing "spasm" to continue. The muscles opposed to those in "spasm" become "mentally alienated," divorced from the patient's mind. "Alienated muscles appear toneless and incapable of voluntary contraction but are never painful or tender indicating that they are not the muscles involved directly by the disease." "Even the tendon reflex of such muscles disappears; alienated muscles become permanently paralyzed and atrophied if steps are not taken early to restore such muscles to action." The third and least important symtom described is "incoordination;" according to the concept, it is due to a "disorganization of the regulating centers."

The various parts of the Kenny concept were investigated by means of chronaxie and action potential studies in forty-nine patients. Muscles called "alienated," muscles in "spasm" as well as normal muscles were explored. The following were found:

A. "Spasm" is not a separate entity but a complex phenomenon. It is the result of: 1) meningeal irritation of the posterior roots, 2) lesions of the dorsal root ganglia, and 3) increase of the normal tonus in healthy muscles opposed to weak or paralyzed muscles.

Muscles in marked "spasm" generally showed normal chronaxie, that is to say they were without any trace of neuromuscular degeneration. The meningeal component of the so-called "spasm" disappears relatively quickly. Irritation of the dorsal root ganglia lasts longer than meningeal reaction. The last and most persistent type of "spasm" is the one due to the increase of the normal tonus in strong muscles. This has nothing in common with true spasm.

B. A paralytic or paretic muscle called "alienated" is always to some degree in neuromuscular degeneration; this is the result of damage to the anterior horn cells. Depending upon the intensity and extent of the lesions, degeneration is more or less marked. It will be indicated by chronaxie measurements. Among the muscles called "alienated," some were in partial and others were found in total neuromuscular degeneration.

C. If among the muscles which have to carry out motion, one or several are paralyzed or paretic, there is necessarily a dis-

turbance in the function of the extremity involved. The automatic regulation of the movement will be interfered with as well as the voluntary movement.

CONCLUSION:

The findings reported here show that the Kenny concept of infantile paralysis can not be accepted.

The so-called "spasm" is not the "most

damaging symptom" of the disease. There is no functional paralysis nor a "physiological block" in the paralytic or paretic muscles. These muscles are not "erased" from the patient's mind but are damaged by anterior horn cell lesions. Moreover there is no clinical evidence of a disorganization of the regulating centers leading to "incoordination."

Tranmatic Shock*

MAGNUS I. GREGERSEN

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The present report constitutes a brief statement of the more important conclusions that my collaborators and I have reached during the past year and a half from our studies on experimental and clinical shock.

Blood pressure is not a reliable index of the severity of injury nor of the degree of shock.

Reduction in blood volume is the initial and determining factor in the train of events preceding shock from hemorrhage or trauma. In both dog and man a reduction of more than 35 per cent leads to shock. Generally speaking a patient in severe shock has lost about two quarts of blood.

Contrary to the view which has been widely proclaimed, hemoconcentration is not a criterion of shock, and the gradual failure of the circulation and appearance of symtoms cannot be ascribed to a progressive decrease in blood volume. The reduction in volume occurs at the time of injury. Thereafter not only the blood volume but the hematocrit and plasma protein level remain essentially unchanged. Accurate measurements of the changes in volume of the traumatized limbs (dogs) show that the "local fluid loss" equals or exceeds the loss in blood volume. These facts together with

other experimental evidence disprove the theory of general increase in capillary permeability. Capillary leakage is limited to the injured region. Elsewhere fluid is absorbed from and not lost into the tissues.

Gradual failure of the circulation after hemorrhage or trauma is related to a progressive decrease in cardiac output (Fick method) which may fall to 10 per cent of the normal, to reduction in oxygen consumption (50 per cent of normal), and to increased A-V oxygen difference (from normal of 4 vols. per cent to 15-20). plete analyses of the blood have revealed extreme changes in arterial CO2, pCO2, pH, lactate, phosphate, and pyruvate. serum potassium remains unchanged untilthe terminal stages are reached. During the last hour before death it may rise to two or three times the normal level. The alterations in the blood are characteristic of the metabolic disturbances produced by They are not peculiar to severe anoxia. traumatic shock.

^{*} This work was done partly under grants from the Josiah Macy, Jr. Foundation and partly under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Columbia University.

Study of the Circulation in Clinical Shock

A. COURNAND, R. L. RILEY, E. S. BREED and D. W. RICHARDS, JR.

Measurements of the circulation have been carried out in 46 cases of injury of various types and in varying degrees of shock, including 25 cases of severe skeletal trauma, 3 cases of chest injury, 8 cases of hemorrhage, 4 cases of burn, and 6 cases of abdominal injury.

Basic measurements employed included:
(a) plasma and blood volumes, (b) arterial pressure (Hamilton manometer), (c) peripheral and central (right auricle) venous pressures, (d) cardiac output (direct Fick technique), (e) arterial and mixed venous blood gases, pH, lactic acid, (f) pulmonary ventilation and respiratory gas exchange, (g) renal clearances. The pressures in the right auricle and mixed venous blood samples were obtained by passing a catheter directly into the right heart.

The description derived from the data obtained conformed to the accepted view

that established shock in the various types of injury studied, was due to a rapid and precipitate failure of the circulation, usually associated with inadequate return of blood flow to the heart. The chief findings were decreased cardiac output, low pressure in the right auricle, low arterial pressure, and decrease in blood volume. With one exception all cases of shock due to skeletal trauma showed hemodilution. Burns and abdominal injuries showed hemoconcentration.

In many cases the effects of blood transfusion and in a few cases the effects of adrenal cortical extract or rapid saline infusion upon the circulation were followed by repeated measurements.

Two individual cases, one of hemorrhage, and one of skeletal trauma (fractured pelvis), are described.

Plasma Clot Suture of Peripheral Nerves

I. M. TARLOV

Young and Medawar have attempted to improve the accepted method of uniting nerves with silk by the use of clots prepared from cockerel plasma and chick embryo extract. The inconveniences involved in the preparation of these materials and, more particularly, the inflammatory and fibrotic reaction resulting in animals of other species, led to the introduction of the technique of autologous plasma clot suture of nerves. The development of a suitable mold in which nerves can be sutured with plasma clot made for more accurate alignment and stronger union of the nerve ends as well as for a broader field of usefulness of the method.

When nerve ends cannot be united without

strain, then plasma clot suture is undesirable since the junction may subsequently come apart. Under these circumstances, following a suggestion by Lt. Col. R. Glen Spurling, tantalum wire (0.003 inches in diameter) has been employed as tension sutures to approximate the nerve ends while accurate apposition is achieved by means of plasma clot. The use of this combined technique eliminates the likelihood of separation of the sutured nerve ends and makes it possible to avoid much of the knuckling of nerve fibers and distortion at the suture site that is apt to follow the classical method of nerve suture by means of thread stitches. The results of plasma clot suture of peripheral nerves are encouraging.

The Production of a Sulfonamide Antagonist and A Sulfonamide · Potentiator by the Tubercle Bacillus

WALSH McDermott and Alice Tracy

When tubercle bacilli (H-37RV) are grown upon synthetic media, bacteria-free filtrates of the culture produce two entirely different effects when added to media containing E. coli and sulfanilamide.

In low dilutions (1-5, 1-10) the filtrates of the tubercle bacillus cultures potentiate the bacteriostatic action of sulfanilamide on E. coli grown in synthetic media.

In higher dilutions (1-50 through 1-1000) the filtrates of the tubercle bacillus cultures completely neutralize the bacteriostatic effect of 7 mg. per cent sulfanilamide on E. coli. The addition of further dilutions of the tubercle bacillus filtrates (1-5000 or more) has no effect upon the usual bacteriostasis of E. coli induced by sulfanilamide.

Two phenomena are manifested here: (1) A sulfonamide-potentiating effect which is present in higher concentrations but which disappears on dilution. (2) Sulfonamide antagonism demonstrable in certain dilutions but masked in the more concentrated dilutions by the potentiator.

The sulfonamide potentiator effect present in the higher concentrations of the filtrates can be shown to be due to the presence of a substance which becomes bacteriostatic only in the presence of sulfanilamide. In contrast to other potentiators and synergists which have been reported, these products of the tubercle bacilli (as filtrates), in the absence of sulfonamide, are stimulants to the growth of E. coli. Yet when added to sulfanilamide solutions, the bacteriostatic power of the resulting combination is considerably increased over the controls containing similar concentrations of sulfanilamide.

The antagonist has properties in common with para-aminobenzoic acid. The tubercle bacilli filtrates have a positive diazo reaction. If the diazotizable substance were para-aminobenzoic acid, it would be present

in amounts averaging 0.03 mg. per 100 cc. of a 6-week culture. When a known solution of this concentration of para-aminobenzoic acid is tested parallel to the tubercle bacilli filtrate, the sulfonamide antagonism produced by both is of the same order of magnitude.

It can be shown that neither of the two phenomena observed in the action of the H-37 filtrates can be reproduced by comparable experiments with purified tuberculoprotein. Both the antagonist and potentiator are ether-soluble. The former is unaffected, the latter almost entirely removed. by acid precipitation. Boiling with sulfurie acid does not prevent either the antisulfonamide or sulfonamide-enhancing effect. It does, however, slightly increase the sulfonamide potentiator effect when the solucontain purified or unpurified tuberculoprotein.

As far as we know, this is the first demonstration of the production of a sulfonamide potentiator by a pathogenic microörganism.

The following abstracts were presented before the Clinical Research meeting May 27, 1943, but publication was withheld.

Vitamin D in human milk, Louis J. Polskin, Benjamin Kramer, Albert E. Sobel. Further studies on penicillin as a chemotherapeutic agent, Martin H. Dawson, G. L. Hobby, K. Meyer, E. Chaffee.

Renal circulation in shock, Henry Lauson. Measurement and recording of intrauterine pressure, Sergei Feitelberg, I. C. Rubin.

Probable mechanism by which somatic changes in certain emotional states are mediated, A. T. Milhorat, S. M. Small, E. J. Doty, W. E. Bartels.

Abstracts Read by Title May 27, 1943

In addition to the foregoing abstracts presented at the Clinical Research meeting held at The New York Academy of Medicine, May 27, 1943, and thereafter submitted for publication, the following manuscripts which could not be presented in the limited time available, were read by title:

- The use of soluble sulformuides in extensive third degree burns. Charles L. Fox, Jr., Joseph Tamerin
- 2. Refrigeration anesthesia and refrigeration therapy, S. Thomas Glasser
- 3. The diagnosis of herniation of the intervertebral disc. Thomas L. Hoen
- 4 Acute perforation of patroduodenal ulcers seen at the Metropolitan Hospital from 1930 to 1941, Walter I, Mersheimer
- 5. Blood volume studies in man, Robert P. Noble, Magnus I. Gregersen
- Sympathectomy in chronic obers and infections of the extrematics, Kenneth C. Peacock
- Local use of sulfathicrole in eye infections with special reference to epidemic kerato-conjunctivitis, Charles A. Turtz
- Correlation of peritoneoscopic findings with clinical and pathological factors, especially of the liver, Leonard P. Wershub
- Sulfadiazine and its sadium compound in the treatment of meningococcie meningitis and meningococcemia, Emanuel Apelbaum, Jack Nelson
- Migraine -a new rationale of treatment, Miles Atkinson
- 11. Resistance of the Rhesus monkey to 90 plus per cent oxygen, Martin Friedrich, David M. Grayzell
- 12. The nature of the solutions in the urine of the excreted products from sulfadia-

- rine therapy, D. R. Gilligan, Walds, McDermott
- 13 Laurence-Moon-Riedl sprömme. S. P. Goodbatt
- 14 Danperous and safe rathway of all mand applications, Berno L. Gere and
- 15. The tubercular polel test. Manager Grazin
- 16. Hypoprother have as in an data hard ered. The effect of erel and garenteral 2 method 14. A haplit by long none the plosphore of every ferm exting each. Norman H. LeTe mean
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- 21. Allergy to sulfousuides, Beet Rather
- 22 Clinical observations on to one temperatures, their therapeutic and path dorseal effects, James R. Liva, P. K. Safford, Jr., M. B. Nathanan, Lamon Weeks Crossman
- 23. Magnesium sulphate in paroxysmal tachycardia, David Scherf
- Electrocardlographic changes after neute loss of blood, David Scherf
- 27. The saline-procaine test in the differentiation of psychogenic "rheumatic" disorders, Otto Steinbrocker, Paul Kuhn

DEATH OF DR. ARNOLD C. KLEBS; ACADEMY LIBRARY CONSULTANT

Land, his home for many years. He had been a Consultant in Bibliography to this Library since 1929.

Dr. Klebs was born at Berne on 17 March 1870 and was the son of Dr. Edwin Klebs (1834-1913), the dis-

tinguished professor of pathology and eminent bacteriologist. (By the way, the textbook on pathology of the elder Klebs is still authoritative on very obscure conditions or lesions). Arnold Klebs was educated at Prague, at the University of Zürich, and in 1895 obtained his medical degree at Basle. Very shortly after that he came to the United States and practised in Chicago. His great interest was tuberculosis and under his editorship Tuberculosis, a Treatise by American Authors appeared in 1909. Dr. Klebs became a United States citizen in 1904. About the year 1909 he returned to Switzerland but made frequent trips to this country.

Fuller accounts of his life have been given, but here it is sufficient to point out his connection with this Academy as well as some of the facets of medical history and bibliography which interested him and about which he wrote. One of the first subjects which occupied his attention was inoculation against smallpox and he published a paper. "The Historic Evolution of Variolation," in the Bulletin of the Johns Hopkins Hospital in 1913. Heft 7 of the periodical, Zur historischen Biologie der Krankheitserreger, Giessen, 1914, constituted a more comprehensive account of inoculation by Klebs. Once he became interested in a subject, he never put it aside for good and all, and I warrant that to his last days he was constantly adding to his bibliography of variolation. Dr. Klebs was an authority on the anatomical work of Leonardo da Vinci and the intricacies of the publications which contain reproductions of the drawings. One paper on Leonardo came out in the

Bulletin of the Society of Medical History of Chicago, in 1916; and another in the Boston Medical and Surgical Journal, 1916.

One will always think of Dr. Klebs in connection with herbals. He probably knew as much as anyone about them in their printed form, and especially about their sources and their family trees. He listed the editions of that Latin poem known as the "Macer Floridus." Also he distinguished three families of editions which he termed the "Herbarns," "Gart" and "Hortus," whilst formerly the knowledge of this large group of herbals was most confused, and they were entered under almost as many as fifteen titles. To bring order out of chaos, meant that Dr. Klebs had to examine and compare scores of copies of different editions. Articles on the subject appeared in 1917 and 1918 in Papers of the Bibliographical Society of America, volumes 11 and 12. And under the title of "Herbal Facts and Fancies" he wrote an introduction to l'Art Ancien's Catalogue of Early Herbals, Lugano, 1925.

Dr. Klebs was a deep student of the earliest printed tracts on the plague; and in 1925 with Mlle E. Droz published from Paris in Viench and in English a little book, Remedies against the Plague ("Scientific Documents of the XVth Century," vol. 1), which contains facsimiles of the three earliest French tracts, a list of the fifteenth century printed texts, and valuable notes. He and Karl Sudhoff collaborated in the book, Die Ersten Gedruckten Pestschriften, Munich, 1926, Dr. Klebs discusses the bibliography of the incunabula; provides a list arranged alphabetically by author, as well as one by year from 1472 to 1501; tabulates the works by place of publication arranged alphabetically; and finally, treating the subject geographically, he has a long section on the history of the printing of these plague tracts.

Dr. Klebs took a wide view of the study of the history of medicine, and anyone who wishes to learn the history of this study and how it has been carried out since it began would do well to consult the article by him. Read at the meeting of the Johns Hopkins Hospital Historical Club on 8 December 1913, his address came out in the Bulletin of the Johns Hopkins Hospital, 1914, with the title, "The History of Medicine as a Subject of Teaching and Research." In the last letter I had from him (28 February 1942), saddened by the long illness of his wife which had become so serious almost five months before, he refers to his ambitions which had not been fulfilled: "Already the last war prevented the carrying out of my plan of returning to the United States for the Balti-

more Institute which I had pushed since 1913 and which I think would have materialized then, but became impossible then." But we know that at Baltimore his ideas have borne abundant fruit.

I think the only paper Dr. Klebs read at this Academy was before the Section of Ophthalmology in 1927. It was published in our *Bulletin* that year with the title, "Historical Perspectives in Ophthalmology."

Dr. Klebs's interest in herbals and plague tracts printed before 1501 has been referred to. But he was not content with these incunabula, and studied those of medicine and science as a whole. His apologia for such work may be found in his address delivered before the Bibliographical Society of America ("Gleanings from Incunabula of Science and Medicine," Papers of the Bibliographical Society of America, Chicago, 1932). It will be seen from the following quotation (p. 58) when, where, and how this began:

I have given to the study of incunabula of medicine and science the better part of the past fifteen years after having been introduced to them in the Surgeon General's Library by Colonel Fielding H. Garrison. I am now engaged with the final revision of a general bibliography of the incunabula of science and medicine, a work which, with the welcome assistance of the New York Academy of Medicine, I hope to bring to an early termination. I have extracted from my records data which I believe can throw a clearer light than hitherto obtainable, on the extent, on the various aspects, and on the paths of dissemination of the earliest scientific literature as it issued from the first European presses.

Dr. Klebs identified and catalogued during 1915-16 the incunabula in the Army Medical Library. He volunteered to catalogue our collection, and in 1929 this was accomplished with the help of Miss Lesta Ford, now Mrs. A. G. Clay. The list with brief entries, prepared by Miss Ford, was published in the *Annals of Medical History* in 1930. He became the acknowledged authority upon such incunabula and his advice was sought by scholars and booksellers the world over. His library, set in the garden at Nyon, became a centre. To it incunabula arrived by ordinary or air mail to be identified or to be looked over by Dr. Klebs before they were purchased by Dr. Harvey Cushing or other friends. His books have been left to the Yale University School of Medicine Historical Library and so will join those of Dr. Cushing. Dr. Klebs was in closest touch with Mr. Victor Scholderer, the expert on

fifteenth century books at the British Museum; and in compiling the list of incunabula of the Royal College of Surgeons of England, the Librarian, Mr. W. R. Le Fanu, acknowledges the help of Dr. Klebs (Annals of Medical History, 1931).

In 1929 Dr. Klebs offered, if encouraged and helped by this Academy, to publish a catalogue of all the incunabula of science and medicine. We accepted with alacrity and it was agreed that the book should be the first publication in the "History of Medicine Series issued under the Auspices of the Library of The New York Academy of Medicine." Even Dr. Klebs did not foresee the difficulties of the task and the length of time it would require; and of course he did not know he would suffer from ill health. We were delighted, however, that his "Incunabula Scientifica et Medica. Short Title List" was published in Osiris, Bruges. 1938, vol. 4, pp. 1-359. He presented the Library Publication Fund Committee with fifty bound reprints (dated 1937) and this title appears first in our History of Medicine Series. Dr. Klebs regretted that the work was not a much fuller one, provided with discussions of the incunabula which fell into various subject classes and with elaborate notes. He also hoped to include a chart referred to in two characteristic letters extracts from which are given below, the first being written to me from Nyon, 19 June 1931:

But joking aside, there is so much to ponder about in these new realisations of human science, that I have had to rewrite great parts of my historical introduction to the incunabula. I hope with some result. . . . I am not giving a paper at the Congress [International Congress of the History of Science and Technology, London, June 1931] but display only an enormous wall map at the Science Museum. On it I have painted in glaring colors the great domains in various chronological aspects, of that of Print and Paper, of Parchment, of Papyrus, and of wood, stone and brick. Not a suggestion of politics, all high brow spirits. It really is quite interesting. Someday we will hang it up in the rare book room. . . .

And speaking of it again in a letter to the late Dr. Linsly R. Williams (30 July 1931) he writes:

... and there are other demands on me which I cannot shirk, such as attendance at the International Congress for the History of Sciences in London where I showed a large map illustrating the diffusion of scientific thought from the beginning to the 15th

century. This will be included in the work and increase its interest, I think. . . .

The "Short Title List" has proved, however, to be a tool of great use to the students of science and medicine of the fifteenth century. Arranged alphabetically under about 650 authors are over 1,000 titles and more than 3,000 editions. Place, date, and printer are given, if known definitely; and references are provided to full descriptions previously published of the incunabula. Also one is told where copies of the numerous editions may be found and consulted. At the end, cross references are given to the various names by which the authors are known.

Dr. Klebs spent many hours in the Library when he came over from Nyon to New York almost every winter, and when here he was sure to look up old friends such as Dr. George Draper and Professor Lynn Thorndike. We are grateful to him for his advice about the Rare Book and History Department. Dr. Klebs knew the true value of books and hated to be called a "bibliophile" if by that was meant one who cared more for the binding and for the rarity of a copy—especially with unopened leaves—than for its contents and its place in the development of knowledge.

ARCHIBALD MALLOCH

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

- Adolph, E. F. Physiological regulations. Lancaster, Cattell, 1943, 502 p.
- American Medical Association. Special Exhibit Committee on Fractures. Illustrated primer on fractures. 5. ed. Chic., Amer. Med. Assoc., 1943, 119 p.
- Ballenger, H. C. A manual of otology, rhinology and laryngology, 2, ed. Phil., Febiger [1943], 334 p.
- Batten, L. W. Health for the young. London, Allen [1942], 176 p.
- Bockus, H. L. Gastro-enterology. Phil, Saunders, 1943, v. 1.
- Bogert, L. J. Nutrition and physical fitness, 4, ed. Phil., Saunders, 1943, 500 p.
- Cole, W. H. & Puestow, C. B. First aid, surgical and medical, 2, ed. N. Y., Appleton-Century [1943], 351 p. [netually 385 p.].
- Colyer (Sir), J. F. & Sprawson, E. C. Dental surgery and pathology. S. ed. London, Longmans [1912], 1067 p.
- Cowdry, E. V. Microscopic technique in biology and medicine. Bult., Williams, 1943, 206 p.
- Eiris, E. J. Dermatosis profesionales. Rosario, Ruir, 1943, 212 p.
- Glaister, J. Medical jurisprudence and toxicology, 7. ed. Edinburgh, Livingstone, 1942, 671 p.
- Ham, A. W. & Salter, M. D. Doctor in the making; the art of being a medical student. Phil., Lippincott [1943], 179 p.
- Hewer, C. L. Recent advances in anaesthesia and analgesia, 4, ed. London, Churchill, 1913, 311 p.
- Hooker, R. W. Ship's doctor. [Autobiography.] N. Y., Whittlesey [1943], 279 p.
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- Howles, J. K. A synopsis of clinical syphilis. St. Louis, Mosby, 1943, 671 p.
- Hurdon, E. Cancer of the uterus. London, Milford, 1912, 188 p.
- Kaufman, W. The common form of niacin amide deficiency discase: aniacinamidosis. Bridgeport, [priv. print?], 1913, 62 p.

- Leonardo, R. A. History of surgery, N. Y., Frohen, 1943, 504 p.
- Loewenberg, S. A. Medical diagnosis and symptomatology, 6, ed. Phit, Davis, 1943, 1181 p.
- Mather, K. Statistical avalysis in Uslagy, London, Methuen, [1913], 217 p.
- Miller, S. C. [et al.]. Textlool of periodontia, 2, ed. Phil, Blakiston [1011], 733 p.
- Moore, J. E. The reeders treatment of syphilis, 2, ed. Springfield, III., Thomas, 1933, 717 p.
- O'Hara, D. Airstorne infection, some etc. servations on its decline, N. Y. Conmonwealth Fund, 1943, 114 p.
- Parsons, R. P. Trail to light; a the region of Jureph Goldberger Andianapolis, Bobb Merrill, [1943], 353 p.
- Pold, J. F. M. & Kenny, E. The Reany concept of infantile paralysis and its treatment. Minneapolis, Bruce, 1840, 366 p.
- Raven, R. W. Surgical circ London, Arnold, [1942], 271 p
- Scoville, W. L. The art of every moding, 7, ed. by J. L. Powers and G. U. Crossen, Phil, Blakiston, [1943], 157 p.
- Shear, C. M. & Krouz, P. P. Mone of of fractures, Phil., Saunders, 1943, 1981 p.
- Strecker, E. A. & Appel, K. E. Discovering ourselves, 2, ed. N. Y., Marmillan, 1943, 431 p.
- Thewlis, M. W. The care of the aged (geriatries). I. ed. St. Louis, Mashy, 1912, 589 p.
- Truby, A. E. Memoir of Walter Reed; the yellow fever episode. N. Y., Hoeber [1943], 239 p.
- Truslow, W. Body poier, Bult., Williams, 1913, 312 p.
- Urbach, E. Allergy, N. Y., Grune, 1943, 1073 p.
- Vaughen, W. T. Primer of allergy, 2, ed. St. Louis, Mosby, 1943, 176 p.
- Voronoff, S. Les sources renouvelées de la vie. [N. Y.], Brentano's, [1942], 301 p.
- Yost, E. American women of science. Phil., Stokes, 1949, 231 p.

Boum, Joseph Leopold, 110 East 53 Street, New York City; born in St. Louis, Missouri, May 13, 1876; died in New York City, June 29, 1943; graduated in medicine from Washington University Medical College, St. Louis, in 1899; elected a Fellow of the Academy, January 3, 1924. Dr. Boehm was a member of the State and County Medical Societies, a Fellow of the American College of Surgeons, a member of the American Urological Society, assistant urologist to Polyclinic Hospital and clinical assistant urologist to Bellevue Hospital.

Fox, Elsir, 384 East 149 Street, New York City; born in Vienna, Austria, January 25, 1885; died in New York City, June 30, 1943; graduated in medicine from Cornell University Medical College in 1911; elected a Fellow of the Academy, October 5, 1916. Dr. Fox was a member of the State and County Medical Societies, qualified under the Workmen's Compensation Law of New York State as a specialist in roentgenology and hacteriology, and was a member of the Bronx Roentgen Ray Society.

LANDSTEINER, KARL, Rockefeller Institute, 66 Street and York Avenue, New York City; born in Vienna, Austria, June 14, 1868; died in New York City, June 26, 1943; graduated in medicine from the University of Vienna in 1891; elected a Fellow of the Academy, January 7, 1932. Dr. Landsteiner

was member emeritus of the Rockefeller Institute where for seventeen years he was active in the field of research, making countless valuable contributions to medicine. He won the Nobel Prize in medicine in 1930, awarded to him in Stockholm.

VAN BEUREN, FREDERICK THEODORE, JR., 65 Fifth Avenue, New York City; born in New York City, February 10, 1876; died in Morristown, New Jersey, March 13, 1943; received the degree of A.B. from Yale University in 1898; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1902; elected a Fellow of the Academy April 7, 1910; and served the Academy as Recording Secretary from 1916 through 1919, as Vice-President from 1925 through 1927, as a member of the Committee on Admission from 1922 through 1927, and as a member of the Committee on Medical Education in 1926.

Dr. Van Beuren was associate clinical professor of surgery at the College of Physicians and Surgeons since 1929 and associate dean at that institution, 1921-34; assistant attending surgeon to Lincoln Hospital, 1910-13, Roosevelt Hospital, 1913-21; attending surgeon to Volunteer Hospital, 1915-17, Sloane Hospital for Women, 1920-38; president of the Morristown Memorial Hospital since 1933; associate visiting surgeon to the Presbyterian Hospital and consulting surgeon to the Elizabeth A. Horton Memorial Hospital at Middletown. He was a diplomate of the American Board of Surgery, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Surgical Association, and a member of the State and County Medical Societies.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



OCTOBER 1943

THE MANAGEMENT OF RHEUMATIC FEVER*

LIEUTENANT COLONIL O. CURRIER McEWEN

Medical Corps, Army of the United States

derstanding the nature of rheumatic heart disease that, in being invited to take part in a series of papers on cardiovascular diseases, I have been asked to diseuss the management, not of rheumatic heart disease, but of rheumatic fever in general. Not many years ago this would scarcely have happened, but today it is generally appreciated that rheumatic heart disease must be thought of primarily in terms of the underlying rheumatic infection. Only in the so-called inactive phase of rheumatic eardiac disease is rheumatic fever per se not an immediate problem, and even here the physician must be constantly mindful of it because of the danger of recurrent attacks.

At this point it may be well to define some of the terms in the sense in which they will be used in this discussion. Rheumatic fever of course requires no definition other than to say that it is used here in its broad sense and embraces all manifestations of active rheumatic infec-

^{*} Given April 28, 1943 in the Refresher Lecture Course in Cardiovascular Diseases Under the Joint Auspices of The New York Academy of Medicine and the New York Heart Association. From the Department of Medicine, New York University College of Medicine, and the 1st General Hospital, U. S. Army.

tion including polyarthritis, fever, carditis, subcutaneous nodules, chorea, rheumatic pleuritis, rashes and others. The adjective acute is, happily, dropping out of use as part of the name of rheumatic fever. Certainly the disease often presents acute and even fulminating phases, but it is essentially a chronic disease extending over a period of months rather than weeks. Rheumatic heart disease is divisible into two principal phases: active and inactive. Active rheumatic heart disease is synonymous with carditis and is the major manifestation of rheumatic fever. Inactive rheumatic heart disease, on the other hand, is the stage of mechanical damage resulting from the previous active inflammation.

In this paper I wish to take up the management of the following: (1) the acute phase of rheumatic fever, (2) the subacute and chronic phases, (3) inactive rheumatic heart disease, (4) certain special forms of therapy, and (5) preventive measures.

Management of the Acute Attack

The acute manifestations of rheumatic fever are mainly polyarthritis, fever and the acute form of carditis. However, others such as chorea, pleuritis or abdominal manifestations may also occur acutely. Good nursing care is a great asset, as in any acute febrile disease accompanied by pain, not only in helping the patient but also in allaying the anxiety of the relatives.

Rest is of the greatest importance. During the acute phase of the disease the physician does not face the difficulty of obtaining the patient's coöperation that he is apt to later in the illness, but rest is often interfered with by pain and orthopnea. Cardiac pain often is aided by an ice bag applied to the precordium but codeine or even morphine may be needed. If dyspnea and orthopnea are present the patient should have a bed of the Gatch type or, if this is not possible, should be propped up with pillows.

The diet of the acutely ill patient should not be forced and should be light, easily digested and liquid or semi-solid. However, as soon as he feels like eating a regular diet may be given. As a rule, fluids should be forced in order to replace water lost through sweating, but in the presence of severe heart failure fluids should be limited to 800 to 1,500 cc. in twenty-four hours depending upon the age and size of the patient.

Polyarthritis and Fever: These are two manifestations easiest to control and can be considered together as they respond to the same meas-

ures, i. e., the so-called antirheumatic drugs. Formerly, much attention was given to cooling baths to reduce fever and proper splinting and local applications for the arthritis; but the antirheumatic drugs are so effective that these earlier procedures are no longer advisable. Indeed they are actually contraindicated as the benefits would be more than offset by the pain resulting from application of the procedures. However, splinting by means of soft pillows properly placed under and around the inflamed joints often is helpful during the hours before the effect of the drugs has been obtained.

The antirheumatic drugs include the salicylates, cinchoninic acid derivatives and aminopyrine. Nothing in the whole field of therapeutics is more dramatic than the response of the fever and polyarthritis to adequate doses of these drugs. The fever falls sharply to normal, other evidences of toxemia disappear and the joint pain and tenderness as well as other signs of local inflammation subside rapidly. Unfortunately, these striking benefits are not accompanied by improvement in the carditis and other rheumatic manifestations such as nodules, rashes, pleuritis and chorea.

Given in adequate therapeutic doses the various drugs are equally beneficial and none accomplishes more than the others. The full therapeutic dose of sodium salicylate, acetyl salicylic acid and neocinchophen is essentially the same: 8 to 10 grams (120 to 150 grains) daily. This amount can be given very satisfactorily in divided doses of 1 gram (15 grains) each every hour for eight to ten doses or until the first signs of toxicity appear. The commonest of these are nausea, vomiting, tinnitus and less often visual disturbances, but if carefully watched for and if the drugs are given in doses no larger than 1 gram each, they should not become very troublesome. Aminopyrine accomplishes no more than the others but dose for dose is much more effective. Thus o.6 gram (10 grains) four times daily is sufficient to obtain an optimum effect. Given in these small amounts it has the advantage of rarely causing nausea or other symptoms. However, its use should be limited to patients under close observation because of its capacity to induce granulocytopenia. Cinchophen is also a moderately effective antirheumatic drug but is inferior to neocinchophen and should not be used because of its tendency to cause hepatitis.

Whichever of the drugs is employed, the general principles are the same. The full therapeutic dose should be given for several days and

then should gradually be reduced—about 0.3 gram (5 grains) daily in the case of aminopyrine and about 1.0 gram (15 grains) daily for the others. If joint pain returns the dose is increased and if toxic signs appear the medication is stopped completely for one day and then resumed in smaller doses.

Carditis: This is, of course, the most serious and important manifes-Caratis. This is, of course, the most serious and important manifestation of rheumatic fever and the one of most concern to the physician. Unfortunately, as has been noted above, carditis is not benefitted by the antirheumatic drugs. Te be sure, a few opinions to the contrary have been recorded. Thus Findlay¹ stated that salicylates given early in polyarthritis protect the heart from damage, and Heninger and McHardy² believed that aminopyrine has therapeutic value in carditis. Unfortunately, however, carefully controlled studies³, ⁴, ⁵ do not bear out these claims and it is accommon contained that a salicylate salicylates given early in polyary that it is accommon contained that a salicylate salicylates given early in polyary that is a salicylate salicylate salicylates given early in polyary that it is a salicylate salicylate salicylates given early in polyary that it is a salicylate salicylate salicylate salicylates given early in polyary that it is a salicylate salicylate salicylate salicylates given early in polyary that salicylates given and it is common experience that pericarditis, cardiac failure and subcutaneous nodules can appear in patients receiving full therapeutic doses of antirheumatic drugs. Probably the inflamed myocardium and valves are helped indirectly by the decrease in heart rate which accompanies the drug-induced fall in fever, but it can be accepted that there is no "specific" beneficial action on the carditis like that on the arthritis. One possible exception is that reported by Boas and Ellenberg⁶ who observed striking decrease in the amount of pericardial fluid in a number of patients with massive pericardial effusions given large doses of salicylates. No published reports by others confirming this observation have yet appeared, but on our Children's Medical Service at Bellevue Hospital the impression has grown that pericardial aspiration has been less frequently necessary since the suggestion of Boas and Ellenberg has been followed.7 Certainly further corroboration is needed but the observation appears to be correct and, if so, marks an advance in the treatment of rheumatic pericarditis. Apparently the action is on the effusion for, as has been already noted, salicylates do not prevent pericarditis. However, this action is important, for a serious danger in pericarditis is cardiac tamponade from too massive an effusion. Other than the salicylates, treatment consists of aspiration of the pericardial effusion. Unless done for diagnostic purposes it is necessary only if the amount of fluid is large enough to interfere with cardiac function and add to respiratory distress. In children, aspiration can usually be done easily by the posterior approach as described by Sutton⁸ but in adults the anterior approach is usual.

Aside from therapy directed against the effusion, the principal measure in the treatment of pericarditis is the same as that of carditis as a whole, namely, complete bed rest. If cardiac pain is distressing, relief is often afforded by an ice cap applied to the precordium but codeine or morphine should be given if necessary.

Heart failure occurring in rheumatic carditis must be treated essentially like that due to heart disease of any other etiological type, with the exception that particular care must be taken to avoid digitalis toxicity. Formerly the view was rather widely held that digitalis was contraindicated in the presence of active carditis. Today there would be few who would make such a statement, for the drug is life-saving in many instances. It is true, however, that toxic arrhythmias may occur as a result of over-digitalization in carditis, perhaps because of the increased irritability of the inflamed myocardium. It should be added that digitalis will not change the eventual course of congestive failure in carditis unless the carditis itself improves. One should not hesitate to use digitalis when indicated, but should give it in somewhat smaller doses than usual and observe the patient carefully for toxic symptoms. Using a preparation of powdered leaf standardized so that o.1 gram (11/2 grains) equals one digitalis unit, a convenient method is to give 0.4 gram as an initial dose followed by 0.2 gram six hours later and then by 0.2 gram morning and afternoon until a therapeutic effect has been noted or suspicious evidence of beginning digitalis toxicity appears. A maintenance dose of 0.1 or 0.2 gram daily will then usually suffice. Other measures, such as restriction of fluid and salt intake and the use of diurctics, are the same as in any other form of congestive heart failure. It is not necessary to consider them in detail here since Dr. Gold has already done so in an earlier paper of this series.

Cardiac Arrhythmias: Arrhythmias occurring during the course of active rheumatic carditis may be of serious import or may have merely symptomatic or diagnostic significance. Auricular fibrillation may occur merely as a toxic arrhythmia and disappear after a few hours to a few weeks either spontaneously or under the influence of quinidine. On the other hand, it may be permanent especially if gross valvular damage has been done in previous rheumatic attacks, and in these instances digitalis must be used. Dr. DeGraff will discuss this subject more fully in a later paper. Premature contractions and prolongation of the atrio-ventricular conduction time, with or without dropping of beats, are transient phe-

nomena in carditis and require no treatment as a rule.

Pleuritis: Early in pleuritis, when pain is present, codeine usually is indicated. Strapping the chest has rarely been necessary in our patients as the pain usually disappears in a day or two as the effusion accumulates. As in the case of pericarditis, thoracentesis need be done only for diagnosis or if the amount of fluid becomes so great as to add to circulatory and respiratory difficulty. The procedure is easily carried out by inserting the needle posteriorly at the point where dulness is greatest. It has been believed that the antirheumatic drugs are of no benefit in rheumatic pleuritis but this warrants re-study in the light of the report of Boas and Ellenberg⁶ to see if they might help limit the amount of the effusion.

Abdominal Manifestations: The therapeutic problem presented by rheumatic abdominal pain is mainly one of diagnosis. This manifestation, which occurs chiefly in children, is not very common, but tends to come early in the disease before other evidences of rheumatic fever have appeared. Thus it is apt to be mistaken for suppurative appendicitis. Rheumatic abdominal pain requires no treatment other than an ice cap and a trial of antirheumatic medication, which seldom helps in our experience. When in doubt about operation, we believe it should be done, for an unnecessary operation probably would not cause any serious harm to the rheumatic subject, whereas failure to operate when needed might prove fatal.

Chorea: This manifestation usually is subacute rather than acute and requires no therapy other than sedation, rest in a quiet room, and sympathetic handling of the emotional instability. For sedation, phenobarbital .03 gram (½ grain) three or four times daily usually is sufficient. When chorea occurs acutely and violently, the patient must have careful nursing to guard against injury from his own uncontrolled movements. In these cases fever therapy should be given either by means of foreign protein injection or one of the more complicated but more efficient electrical methods. The aim of treatment is to induce a rise of temperature to 104°-105° F. and maintain it three to five hours. Depending on the severity of the chorea, two to twenty (average six) treatments may be necessary. Detailed descriptions of the techniques cannot be given here but can be found elsewhere. 9, 10, 11, 12 Fever therapy should be used also in less violent chorea if it does not respond satisfactorily to the usual conservative measures. Whether fever therapy given

early tends to minimize the development of cardiac damage is not fully answered but I believe is doubtful. Arsenic and salicylates, which formerly were used, have been found to be of no benefit.

Subcutaneous Nodules and Rashes. These manifestations are not influenced by medication and require no treatment other than that of the disease in general.

MANAGEMENT OF THE SUBACUTE AND CHRONIC PHASE

This phase of rheumatic fever is essentially one of low-grade carditis accompanied usually by mild fever and anemia and often by other rheumatic manifestations such as rashes and subcutaneous nodules and by occasional vague joint pains.

Rest is again the principal therapeutic measure in association with supportive care and the treatment of symptoms as they arise. Unfortunately, the enforcement of rest is often a very real problem at this stage of the disease, for the patient usually feels quite well. Hence the patient and his parents must understand the nature of the disease if the necessary cooperation is to be obtained. It is also important to establish certain criteria which must be met before the disease can be considered inactive and the patient ready to be out of bed. We have found the following requirement satisfactory: (a) normal rectal temperature, pulse and leukocyte count for ten consecutive days in the absence of antirheumatic drugs; (b) freedom from all manifestations of rheumatic activity such as rashes, subcutaneous nodules and joint pain; (c) normal auriculoventricular conduction time; (d) satisfactory increase in weight and in erythrocyte count and hemoglobin; (e) return of the erythrocyte sedimentation to, or nearly to, normal; and (f) satisfactory improvement in the patient's general condition. When improvement has advanced to this point, the patient may begin to sit up in a chair for a half hour morning and afternoon and this may be increased about a half hour each day until most of the day is spent out of bed. Walking on the level may then be gradually allowed and finally stair-climbing may be undertaken. Needless to say, if signs of increased rheumatic activity appear at any time, bed rest must be temporarily resumed. One cannot prophesy how long will be required for a given patient to progress from the start of his illness to complete quiescence of the rheumatic infection, but in a group of 72 patients reported by Swift13 the range was from 30 to 255 days with an average of about four months.

Diet in the subacute phase of rheumatic fever plays a role second only to rest. The therapeutic aim, as in tuberculosis, is to support the patient as effectively as possible while he is overcoming his long-continued, systemic infection. Therefore, as soon as the acute stage has subsided, a nourishing diet should be given. There are no particular requirements other than that the diet shall be well balanced and sufficiently varied and appetizing to encourage the patient to eat. As improvement occurs, the lack of exercise coupled with good food may lead to too great an increase in weight, and the diet may have to be reduced.

Anemia of the secondary type almost always develops if care is not taken to combat it. Ferrous sulphate 0.3 gram (5 grains) t. i. d. after meals is very satisfactory for this purpose. Very rarely it may be advisable to give one or two transfusions of whole blood if anemia is progressive in spite of iron therapy. If so, not more than 200 to 400 cc. should be given at a time and administration should be slow in order to avoid any sudden increase in blood volume with resultant cardiac embarrassment.

General care is an all inclusive term in a long-continued disease like rheumatic fever but certainly special thought must be given to the patient's morale and that of his family. Psychotherapy of the type that can be practiced by every physician is particularly important, for the patient is apt to become morose, introspective or spoiled if not wisely handled. Occupational therapy is an exceedingly useful adjunct and makes the problem of insuring adequate bed rest less difficult. One of the best forms of occupational therapy for rheumatic children is home schooling, for these patients are apt to miss much of their regular school work during their repeated rheumatic attacks. This is made more serious by the fact that they probably must earn their living later in life by types of work which do not require physical exertion and for which they will be unfitted if they are not educated.

Convalescent care in special types of institutions has increased in recent years. In the case of rheumatic fever, these institutions must provide complete bed rest if they are to be suitable for the patient who still has the active disease. If they do not, they are satisfactory for the patient whose rheumatic fever has reached the completely quiescent stage but may actually do harm to those with active infection through requiring too much physical exertion. In other words, rest should be of the type provided in sanitoria for tuberculous patients. One of the disadvantages

of institutional convalescent care for rheumatic patients is the danger of ward epidemics of respiratory infections with resultant rheumatic recrudescences. For this reason the "cottage" type of convalescent institution should offer advantages over those based on a system of larger wards.

THE MANAGEMENT OF INACTIVE RHEUMATIC HEART DISEASE

This must be considered separately for patients with and without symptoms of congestive failure. In the absence of symptoms no therapy is required for the heart disease per se, and proper management consists of measures designed to prevent recurrent attacks of rheumatic fever, and seeing the patient at intervals of three to twelve months to observe his progress and give advice where it is needed. In these patients we believe that any but the most strenuous competitive sports may be allowed and, indeed, encouraged; for too close supervision and restriction can lead to the development of cardiac neuroses.

If symptoms of congestive failure appear, the physician must decide whether they are due to the return of active rheumatic carditis, failure from purely mechanical cardiac insufficiency, or a cardiac neurosis. If active carditis is present, management immediately becomes that of the acute or of the subacute and chronic phases as already discussed. If purely mechanical factors are at play, management consists of restrestriction of fluid, and the use of digitalis and various diuretics as has been discussed by Dr. Gold in an earlier paper of this series.

SPECIAL FORMS OF THERAPY

In addition to the important general principles in the treatment of rheumatic fever which have been considered above, a number of special forms of therapy warrant brief discussion.

Specific Therapy. This has been attempted by various means but all have proved to be valueless. Serum therapy of rheumatic fever was tried by Menzer¹⁴ in 1902 and more recently by Small.¹⁵ Carefully controlled studies, ^{16, 17, 18} however, showed no beneficial effect. Vaccine therapy introduced by Swift and his coworkers, ^{13,29,21} at first seemed promising but more prolonged observations were disappointing²² and it was found that vaccines may be actually harmful. Convalescent serum and transfusions of whole blood obtained from donors convalescent from rheumatic fever also have been tried without success. ^{23, 24}

Sulfanilamide, naturally enough, was tried in the treatment of rheumatic fever soon after its effectiveness against hemolytic streptococci was demonstrated. Its value in prophylaxis will be discussed below but it is useless or even harmful once the disease has begun.^{25, 26, 27}

Climatotherapy was suggested as a rational procedure in rheumatic fever by the well known fact that the disease is less common and less acute in the southern United States than in the north. Because of this, Coburn²⁸ transported a group of rheumatic children from New York to Puerto Rico. He noted distinct improvement while they were in this subtropical climate but relapses occurred soon after the return to New York City. Jones and his collaborators²⁹ obtained much less striking results in a group transported from Boston to Miami but the evidence seems to indicate that climatotherapy is valuable in selected cases of long-standing, low-grade activity if the expense involved can be borne.

Physical therapy has at least one important application in rheumatic fever in the form of fever therapy for severe chorea as noted above. 9,10,11,12 Another possible application is the use of x-ray therapy in the treatment of persistent low-grade carditis as suggested by Levy and Golden, 30,31 This requires confirmation by others, however, before its value can be assessed with any certainty.

Eradication of foci of infection, especially infected tonsils, has been widely used and seems a logical procedure in view of the frequency with which rheumatic attacks follow tonsillitis. Among those advocating tonsillectomy, a few³² recommend it early in the acute phase of rheumatic fever but most believe it to be dangerous at that time and allowable only during convalescence. Careful statistical studies, on the other hand, reveal no evidence that tonsillectomy favorably affects the course of rheumatic fever and indicate that once that disease has appeared, rheumatic relapses occur with approximately equal frequency whether or not tonsillectomy is performed.^{33,34,35,36} There is even less to suggest that treatment of other localized infections, such as those of the teeth and sinuses, exerts any direct benefit on rheumatic fever. Thus it is our practice to perform these various operations only if the respective infections are such that they should be eradicated for the benefit of the patient's general health, irrespective of his rheumatic fever.

PREVENTIVE MEASURES

Most of the important recent advances in the care of the rheumatic

subject are in the field of preventing recurrent attacks. Although some of these still require the test of time for a final evaluation, they appear to be very promising. The great importance of such measures is clear when one takes into account the fact that rheumatic fever seldom is fatal in the first attack and that the chief hazard is one of progressive cardiac damage incurred in each subsequent attack.

Avoidance of Infections: The accumulating evidence that hemolytic streptococcal infections in rheumatic subjects are apt to be followed by new attacks of rheumatic fever, clearly indicates the importance of avoiding them in every possible way. Even in the hospital, nurses and interns must be warned of the danger of placing patients with tonsillitis near those convalescing from rheumatic fever, and visitors and attendants with respiratory infections must be kept away. In the home, pains must be taken to make other members of the family understand that what is just a simple sore throat to them may be a potential attack of rheumatic fever to the rheumatic subject and they must be taught simple isolation techniques.

Tonsillectomy: It was noted above that tonsillectomy does not seem to reduce the likelihood of recurrences once rheumatic fever has appeared, but Kaiser's studies³⁶ suggest that the operation tends to prevent the disease in those who are not already rheumatic subjects. On the supposition that this is correct we believe it advisable to recommend tonsillectomy for children with a family history of rheumatic fever, especially if they are liable to sore throats.

Climate: For the reasons already mentioned, it seems probable that rheumatic patients may escape further attacks by living in certain subtropical areas. For those who cannot make their permanent homes in the south, a sojourn there may be beneficial during the winter and spring months when rheumatic fever is most prevalent in the north. Obviously this is not a practical measure for many because of the cost.

Sulfanilamide: Although this drug does not favorably influence the course of disease once rheumatic fever or its antecedent hemolytic streptococcus infection has started, the use of sulfanilamide to prevent the "trigger" infection is one of the most promising prophylactic measures yet attempted for this disease. Introduced independently by Thomas and France³⁷ and Coburn and Moore²⁷ in 1939, the method has been studied subsequently by others. ^{38,39,40} The aim is to give a daily maintenance dose of sulfanilamide throughout the year or during the period

from December to the end of May when rheumatic fever is most apt to occur. A convenient method is to give two doses of 0.6 gram (10 grains) daily—morning and evening. Within limits the size of the patient is of minor importance, though Kuttner³⁹ recommends increasing the dose to between 1.3 and 2.0 grams (20 to 30 grains) daily for children weighing more than 75 pounds. In terms of concentration of sulfanilamide in the blood, a level of 2 mg. per cent appears to be adequate. Thomas⁴¹ has summarized the total experience of the various studies referred to above as follows: in a total of 648 patient-seasons there have been six attacks of recurrent rheumatic fever, whereas the experience in control groups of rheumatic children not receiving sulfanilamide prophylactically would lead one to expect an incidence of 130 attacks. For the most part, the children have tolerated the drug well. Nausea, rashes and fever have been the chief toxic manifestations but only Stowell and Button³⁸ found it necessary to discontinue medication because of these symptoms in any large number of patients. They also reported the one death, which was due to agranulocytosis. There is general agreement that toxic manifestations appear chiefly from the 14th to the 50th day. Therefore the closet observation of patients under treatment is necessary during that period but subsequently may be somewhat less painstaking. Because of the newness of the procedure and the possible occurrence of toxic symptoms it would be wise for anyone planning to use sulfanilamide in this way to study carefully the original articles referred to above. As yet there has been no report of experience with other drugs of the sulfonamide series.

believed that the administration of salicylates to rheumatic patients who acquired sore throats would prevent the development of rheumatic flare-ups. In this country, however, little attention has been paid to this suggestion because of the known inability of the antirheumatic drugs to affect the course of carditis. Recently, however, Coburn and Moore⁴³ have reported favorably their experience with it. They gave 4 to 6 grams (60 to 90 grains) of salicylate daily during the period of sore throat and for several weeks thereafter. Among forty-seven rheumatic patients receiving this therapy only one rheumatic flare-up occurred, while among 139 control patients there were 57 such flare-ups. The procedure clearly needs further corroboration but has promise of being of great importance. It is, of course, harmless, but the physician apply-

ing it assumes a very real responsibility to observe the patient with the greatest care to make sure that rheumatic fever actually is not occurring but with its more outspoken symptoms masked by the drug.

Vaccines: The lack of success with vaccines in treating rheumatic fever has already been mentioned, and their value in preventing new attacks is also very doubtful. Recently⁴⁴ it has been reported that rheumatic children given a filtrate prepared from hemolytic streptococci had fewer subsequent attacks than did untreated children. Results with ordinary vaccines²² and our own limited experience with filtrates,²³ however, have been disappointing and confirmation is needed.

General Hygiene: In conclusion I wish merely to refer to the relative infrequency of rheumatic fever among the well-to-do compared with its incidence among the poor. This indicates the bearing that poor housing, crowding and poor general hygiene have on the disease and suggests that slum clearance projects and similar sociological advances will do much to help reduce the importance of this dread disease.

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THE TREATMENT OF RHEUMATOID ARTHRITIS INCLUDING GOLD SALTS THERAPY*

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RESERVED HEUMATOID arthritis is a common disorder of the joints, almost never causing death but frequently causing prolonged disability. Although it is considered to be an infectious disease, its exact cause is still unknown. Rarely does one see spontaneous recovery once the disease is well established. In the past, available treatment did not produce satisfactory results, but since the advent of gold salts therapy we may expect an inactivation of the disease in about 50 per cent of properly treated cases.

Rheumatoid arthritis starts insidiously, or acutely with signs of active infection. Females between 18 and 40 are most commonly affected, although no age is exempt. There are soft fluctuant swellings of the joints, usually symmetrical. The erythrocyte sedimentation rate is usually elevated. There is apt to be considerable loss of weight, a hypochromic anemia and marked muscle wasting. The x-ray sooner or later shows erosions of cartilage and subchrondral bone, with generalized decalcification. While this paper deals exclusively with treatment, it is important to emphasize that the treatment outlined is designed only for bonafide rheumatoid arthritis. One is not justified in administering gold salts unless the diagnosis of rheumatoid arthritis is well established.

THE EXAMINATION

In order to treat properly the patient with rheumatoid arthritis, the examination must include the following essentials:

- 1. A complete medical survey.
- 2. An orthopedic survey especially from the point-of-view of body mechanics.
- 3. A specific search for foci of infection.

^{*} Read March 26, 1943 in the Friday Afternoon Lecture Series of The New York Academy of Medicine.

- 4. A record of the amount of disability in each affected joint.
- 5. Laboratory data:
 - a) Erythrocyte sedimentation rate.
 - b) Complete blood count.
 - c) Urinalysis
 - d) Blood uric acid.
 - e) X-rays of the joints most involved.
 - f) Culture of synovial fluid when a specific infectious arthritis is suspected.

Not only must the joints be examined, but the patient must be viewed as an internal medical problem. She is suffering with what appears to be a chronic infectious disease. Anything that may be unearthed in the medical examination of the patient is important as a factor in her constitutional resistance. Thus we still search for foci of infection especially in the sinuses, tonsils and teeth, but are less optimistic than in the past as to the value of the treatment of these foci in rheumatoid arthritis. Foci of infection are treated with the idea of improving the patient's general health rather than on the assumption that thereby we are removing important causative factors. The blood uric acid must always be determined in order to help eliminate the atypical case of gout. The rest of the laboratory data is purely non-specific in nature; unfortunately there is no diagnostic blood manifestation in rheumatoid arthritis.

TREATMENT

Treatment falls into five categories.

- 1. Constitutional rehabilitation.
- 2. Gold salts therapy.
- 3. Transfusions of whole blood.
- 4. Prevention of deformities.
- 5. Treatment of deformities.

When the disease is active, it is important that all five forms of approach be instituted simultaneously. One is not justified, for example, in administering gold salts therapy without attention to the patient's general health problems. Likewise, in the long run it is futile to treat by complicated orthopedic procedures, the deformities already present, if the disease is allowed to continue without an attempt at inactivation by medical measures.

CONSTITUTIONAL THERAPY

Constitutional therapy alone has in the past produced a certain percentage of arrests in rheumatoid arthritis. Certainly it is an essential part of any therapeutic program. There is space here for only the barest statement of general principles.

- The treatment of any derangement found after a thorough internal medical survey. It is futile for example, to expect a good result from any form of treatment if the patient has an uncontrolled diabetes.
- 2. Rest. Both general (physical and emotional) and local. The axium that infection is an indication for rest holds true in rheumatoid arthritis. If there is fever, the patient must be put to bed. As long as the disease is active he must be encouraged to rest as much as possible. Emotional fatigue is likewise important. Local rest of severely affected joints with splints, braces or casts is often indicated.
- 3. Proper nutrition.
 - a) Adequate teeth for chewing.
 - b) A well balanced high vitamin diet. There is no specific diet for rheumatoid arthritis.
- 4. Proper gastrointestinal function.
 - a) Hydrochloric acid when indicated, since hypochlorhydria is a common finding.
 - b) Proper bowel elimination.
- 5. Iron by mouth for the hypochromic anemia.
- 6. Correction of postural defects, especially weak feer.

GOLD SALTS THERAPY

The modern history of the use of gold salts in medicine probably started with the observations of Robert Koch, that gold cyanide in dilutions of one in two million inhibited the growth of tubercle bacilli in vitro. It was natural that following this observation, gold salts should be used therapeutically in experimental tuberculosis and subsequently in tuberculosis in human subjects. Eventually it became one of the standard treatments of discoid lupus erythematosus, apparently on the false assumption that this disorder was tubercular in origin. Its use in arthritis probably arose from the fact that some schools of European

| Gold Salt | Percentage of Metallic Gold | Proprietary Name | Water Solubility |
|---------------------------|-----------------------------|---------------------|---------------------|
| Gold Sodium Thiosulphate* | 37% | Sanocrysin | Yes |
| Gold Sodium Thiomalate | 50% | Myocrisine | Yes |
| Gold Thioglucose | 50% | Solganol B | Yes |
| Gold Calcium Thiomalate | 44.4% | | No |

50%

Lauron

No

TABLE I
GOLD SALTS IN COMMON USE

Gold Glyco Thioanilide.....

thought entertained the theory that rheumatoid arthritis was also tubercular in origin. It was natural therefore for them to try the effect of gold salts therapy. The idea was popularized by Forestier whose first reports appeared in 1929.

The indications for gold salts therapy are only two, a positive clinical diagnosis of active rheumatoid arthritis and a duration of the disease longer than three months. One is not justified in using a form of treatment which has at times serious toxic repercussions, unless the disease is well established, and is not likely to clear up spontaneously. It is commonly observed that patients with acute infectious arthritis will spontaneously recover in 60 per cent of the cases during the first three months of illness. Until this period has elapsed, gold salts therapy should be withheld.

There are four contraindications for the use of gold salts therapy. It should never be used in that form of arthritis which appears to be rheumatoid in type, but is associated with lupus erythematosus disseminatus (in contradistinction to the discoid type when gold salts may be used). Its use in this syndrome is extremely dangerous. It also should be avoided where there is an associated acute rheumatic fever, with or without carditis. Likewise, renal impairment or blood dyscrasias should contradict its use.

The gold salts in common use today are listed in Table I together with the percentage of metallic gold in each compound, and whether or not it is soluble in water.

Only the first three listed are available for general use, the last two

^{*} Double salt.

being as yet available for experimental purposes only. Gold calcium thiomalate¹ (Merck) and gold glyco thioanilide (Endo) are insoluble in water and have been developed recently, on the assumption that this insolubility makes them less rapidly absorbed and less toxic in effect. This has proven to be the case in laboratory animals and a preliminary survey of our patients treated with these insoluble compounds appears to bear out this prediction.

All compounds are given intragluteally except the thiosulphate, which is usually given intravenously. The administration of gold salts, whether soluble or insoluble, calls for about the same dosage schedule. It has been found by most workers in the field that doses over 50 mgm. a week increase the rate and duration of toxic manifestations. A general summary of the method of administration is as follows:

Dosage Schedule:

1st dose 2nd dose 3rd dose Thereafter

25 mgm. Gold Salts50 mgm. Gold Salts50 mgm. Gold Salts

10 mgm. Gold Salts

Interval Between Injections:

3 to 7 days

Total Dosage (one course):

1000 to 2000 mgm.

Interval Between Courses:

2 to 3 months

Total Courses:

1 to 3

The various factors will naturally be modified by the patient's individual response. If the first course of gold salts does not produce a satisfactory result, one is not justified in giving a second course. On the other hand if the first course results in a definite arrest of the disease, then one must insist on administering a second and even a third course in order to avoid a subsequent relapse.

One great drawback in the use of gold salts therapy is the frequent manifestation of toxicity or hypersensitivity. The reactions most commonly observed and in approximately the order of frequency, are as follows:

- 1. Pruritus
- 2. Dermatitis

TABLE II

URINARY EXCRETION OF GOLD FOLLOWING SUBCUTANEOUS
INJECTIONS OF GOLD SODIUM THIOMALATE

| Case | Date | Administration of Gold Salt (Mgm.) | Volume 24 Hr. Urine Cc. | Urinary Excretion As Au In 24 Hr. (Mgm.) |
|----------------|----------------|------------------------------------|----------------------------|--|
| O. J., | March 14-15 | | 1,125 | 0 |
| female, | 20-21 | | 925 | ŏ |
| age 35 | 21-22 | 5.0 | 840 | 0.38 |
| years. | 27-28 | | 1,000 | 0.08 |
| • | 28-29 | 10.0 | 935 | 0.15 |
| | April 3-4 | | 1,125 | 0,08 |
| | 4-5 | 25.0 | 780 | 0.30 |
| | 10-11 | | 860 | 0.13 |
| | 11-12 | 25.0 | 810 | 0 42 |
| | 17-18 | | 720 | 0,23 |
| | 18-19 | 25.0 | 1,060 | 0.44 |
| | 24-25 | | 1,000 | 0.18 |
| | 25-26 | 25.0 | 770 | 0.28 |
| | May I-2 | | 800 | 0.24 |
| | 2-3 | 25.0 | 700 | 0.75 |
| | 8-9 | | 510 | 0.32 |
| | 9-10 | 25.0 | 600 | 0 40 |
| M. W., | Dec. 20, 1939 | | | |
| female, age 38 | April 26, 1940 | | 330 | |
| years. | April 25-26 | | 370 | 0.36 |
| | 26-27 | 25.0 | 300 | 0.51 |
| | 27-28 28-29 | 1 | 690 | 0.24 |
| | 29-30 | | 880 | 0.25 |
| | 30-May 1 | | 900 | 0.17 |
| | May 1-2 | | 750 | 0 35 |
| | May 1-2 2-3 | } | 870 | 0 34 |
| | 3-4 | 25.0 | 1,250 | 0.24 |
| | 4-5 | 20.0 | 500 | 0.47 |
| | 5-6 | | 250 | 0.42 |
| | 6-7 | | 825 | 0.42 |
| | 7-8 | | 800 | 0,36 |
| | 8-9 | | 775 | 0.34 |
| | 9-10 | | 560 | 0.24 |
| | 10 | 25.0 | | } |

- 3. Stomatitis
- 4. Renal irritation
- 5. Leukopenia
- 6. Thrombopenia without, or with purpura
- 8. Toxic hepatitis

There are other rarer toxic reactions not mentioned above. The in-

TABLE III

URINARY EXCRETION OF GOLD AFTER STOPPING THE ADMINISTRATION OF GOLD SODIUM THIOMALATE FROM 60 TO 300 DAYS

| Case | No. Days Since Last Dose | Last Dose (Mgm.) | Total Gold Salt Given | Volume 24 Hr. Urine Cc. | Urinary Gold Excretion (Mgm.) |
|----------------------------|---|--|---|--|--|
| I 2 3 | 60 300 102 | 25 10 10 | 340 340 493 (Second Course) | 1,500 1,200 1,000 | 0.13 0.01 0.16 |
| 4 5 6 7 8 9 | 90 210 240 270 135 100 98 90 | 30 25 25 25 25 50 30 50 | 575 200 200 200 1,100 410 1,005 85 | 840 530 1,200 1,675 1,400 860 1,370 1,650 | 0.16 0.04 0.03 0.00 0.09 0.10 0.17 0.08 |

cidence of toxic reactions of all types in one series of our cases using only gold sodium thiomalate, was 38 per cent. However, only in 10 per cent of the cases was the reaction serious enough to warrant stopping the therapy. We have observed only one death in well over 1000 cases treated with various gold compounds. The "toxic" reactions are probably in the main hypersensitivity reactions and not the result of direct parenchymatous damage.

In order to minimize the frequency of these reactions, certain precautions must always be observed. They may be listed as follows:

- 1. Before each injection:
 - a) Question the patient as to itching of skin.
 - b) Examine the skin for a rash or purpuric spots.
 - c) Examine the mouth for stomatitis.
 - d) Examine the urine for albumin and red blood cells.
- 2. Every two weeks:
 - a) A white blood count and differential count.
 - b) A hemoglobin determination.
- 3. Additional precautions in suspect subjects:
 - a) Addis counts.
 - b) Platelet counts.

EFFECT OF CONTINUING ADMINISTRATION OF GOLD SODIUM THIO-MALATE ON THE BACTERIOSTATIC POWER OF THE SERUM IN VITRO

| Case No. | Gold Salt (Mgm.) | Bacteriostasis (Col./Cc.) |
|----------|-----------------------|---------------------------------------|
| 2 | 0 50 115 155 | 700,000* 1,600,000 5,000 160 |
| 3 | 15 119 286 | ∞1:1,000 dil. 10,150 60 |
| . | 0 60 210 | ∞1:1,000 dil. 21,000 210 |
| 11 | 0 85 310 | ∞1:1,000 dil. 10,000 160 |
| 18 | 0 115 415 | ∞1:1,000 dil. 17,800 178 |

^{*} Vaccines previously administered.

THE EXCRETION OF GOLD SALTS

It has been shown by us² and by others, notably Freyberg,³ that injected gold is stored in the body, and excreted extremely slowly. The pathway of excretion is by way of the kidneys and intestinal tract. When soluble compounds of gold are administered, the excretion is mainly by way of the urine (Table II).

The reverse situation obtains in the case of the insoluble compounds for Freyberg³ has shown that more is excreted through the stool than through the urine. The important fact to stress, however, is that the total excretion by both urine and stool during the time of administration is very much less than the actual amount injected. This stored gold is released at a more or less regular rate for a period which may extend over ten months or more after the last dose of a course of gold salts has been administered. See Table III.

Mode of Action

The mechanism of action of gold salts is unknown. It was first thought that they acted by stimulating the reticulo-endothelial system or by stimulating the agglutinin content of the blood, but it has been shown by us⁴ and others that no such phenomena can be demonstrated after the administration of gold salts. It can, however, be shown that the bacteriostatic powers of the serum are markedly increased following the administration of gold salts, when tested against ordinary laboratory organisms such as streptococci and pneumococci. See Table IV, where a beta hemolytic streptococcus was used.

Unfortunately, although rheumatoid arthritis is considered to be an infectious disease, we do not know the offending organism, and therefore cannot test the bacteriostatic powers of the serum of gold treated patients against organisms known to be causally related to rheumatoid arthritis. It is possible, but has not been proven therefore, that gold salts act through their direct bacteriostatic effect, when the gold content of the blood, which can be quantitatively determined,⁵ reaches an adequate level.

RESULTS OF TREATMENT WITH GOLD SALTS

In our series of 264 cases of rheumatoid arthritis treated with gold sodium thiomalate, a remission of the disease was observed in 54 per cent. Most of these received only gold salts therapy, transfusions and adequate constitutional therapy being omitted for economic and other reasons. All had the disease over six months, and most over one year. In those who responded satisfactorily, the favorable turn came about the eighth week of treatment. The sedimentation rate usually slowly returned to normal, the patient gained weight, the hemoglobin rose, and the joint manifestations resolved. Subsequent relapse occurred in about 21 per cent of these subjects, leaving 33 per cent completely arrested after a follow-up period of at least one year. When adequate constitutional therapy and transfusions supplement gold therapy, in situations where the hospital or home environment and economic status allow this, the permanent arrests are well over 50 per cent of the cases treated.

Similar results were obtained in other series treated with other compounds of gold. We cannot observe any important difference in the

therapeutic effectiveness of the various gold salts. We do feel, however, that the insoluble compounds are definitely less toxic. An analysis of our cases, not yet complete, appears to bear out this statement.

Transfusions

It has been observed that repeated transfusions preferably every seven days for ten or twelve weeks, have beneficial effects on rheumatoid arthritis patients, often to the point of initiating a remission of the disease. Exactly what mechanism is responsible for this is difficult to say. The transfusions may be beneficial due to the fact that they ameliorate the hypochromic anemia that is usually present, that they correct the disturbed albumin-globulin ratio commonly observed in severe cases, that they produce a form of non-specific protein shock reaction, and lastly passively transfer resistance to the recipients. The transfusions may be given when the patients are intolerant of gold salts, or during the course of the administration of these salts.

TREATMENT OF DEFORMITIES

Space will not permit a thorough discussion of the methods by which we might prevent deformities in rheumatoid arthritis. The subject is of great importance, however. There is nothing more crippling than the flexion deformities observed in the weight-bearing joints, especially the knees, in rheumatoid arthritis. Most of these can be corrected during the first six months of deformity by the application of a series of plaster casts. These casts are preferably applied without forceful correction of the deformity. After two weeks a new cast is applied to take advantage of the correction thus obtained through muscle relaxation. Those deformities which have persisted over a year will usually not respond satisfactorily to anything but open operation.

The rehabilitation of arthritic derelicts is a field of orthopedic surgery, that has hardly been explored. It is surprising what can be done with careful planning and patience. We have recently seen a 38 year old woman return to a self-supporting job, after 15 years in a City hospital, after an arthrodesis of one knee and a posterior capsulotomy operation on the other.

SUMMARY

A simultaneously applied program of constitutional rehabilitation,

gold salts, whole blood transfusions, and prevention and treatment of deformities, will produce satisfactory results in over half of the patients with rheumatoid arthritis. Gold salts are an essential part of this program, but it cannot be too strongly emphasized that gold salts are capable of producing serious toxic reactions and therefore must be administered with caution. When properly given, however, their good effects far outweigh the risk involved.

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CARDIOVASCULAR PROBLEMS IN THE WAR: HYPERTENSION AND THE NAVY*

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Medical Center at Bethesda, Md., and a tour of war casure ualties at the U. S. Naval Hospitals at Oakland, Treasure Island, Mare Island and San Diego in December, 1942, have impressed me with the many important implications which hypertension has for the Navy. These implications often differ from those in civilian medical practice.

Officer candidates for the Navy, or even ordinary recruits, bring to the doctor an examinee who is far more tense than one generally sees in private practice. An officer receives an annual physical examination, one for promotion, one before proceeding out of the continental United States, or before assignment to a task force. The findings mean far more to the officer than to the man in civilian life. His whole future, his lifelong ambition is to make that promotion, to command or be in a task force. He appears tense and nervous far beyond the degree seen anywhere else. It is hard for him to relax and there is no doubt his blood pressure is unnaturally elevated and his heart rate increased. Borderline blood pressure candidates are examined and re-examined and sent from one internist to another. When finally a young aviation cadet comes to the cardiologist his arterial tension has climbed, keeping apace with his nervousness. In the present war when thousands are examined daily the situation just described is indeed frequent.

The Manual of the Medical Department of the U. S. Navy, Section 1490, states that a cause for rejection of applicants for enlistment is a "hypertension evidenced by a persistent systolic blood pressure above 150. In persons under 25 years of age, a persistent systolic pressure of or above 140 or a persistent diastolic pressure of 95 or over before or after exercise, is a cause for rejection." Section 1483 reads: "In considering the blood pressure, due regard must be given to the age of the

^{*} Read January 21, 1943 at a Joint Meeting of the Section of Medicine of The New York Academy of Medicine and the New York Heart Association.

applicant and to physiological causes, such as excitement, recent exercises, and digestion. The condition of the arteries, the tenseness of the pulse, and the degree of accentuation of the aortic second sound must be taken into consideration, as well as the relation between the systolic and diastolic pressure. No applicant will be rejected as a result of a single reading. When the blood pressure estimation at the first examination is regarded as abnormal, or in case of doubt, the procedure will be repeated twice daily (in the morning and in the afternoon) for a sufficient number of days to enable the Examiner to arrive at a definite conclusion."

Let us apply ourselves to actual cases. The first blood pressure reading of a young aviation cadet candidate was 170/90 but this finally dropped to 136/86. The cadet was accepted after tests showed his circulatory system to be normal. An officer candidate of 40 had a blood pressure of 180/98 but the lowest reading obtained after repeated examinations was 154/90. He was rejected, due consideration having been given to the duties he would have had to perform and his qualifications. Both candidates were of excellent physique. The young aviation candidate was accepted for the Navy, yet as clinicians we know he is an actual hypertensive, a pre-hypertensive, or a potential hypertensive.1-5 A patient possessing a definite hypertension at one time may present a normal blood pressure at another. He still has a hypertension. The blood pressure of hypertension patients are notoriously labile.6,7,8 The insurance companies realize this and in fact are now reversing their former policy and taking into consideration high figures even if transient, for their statistics show that persons with transient high readings tend to become permanent hypertensives in later years.6,7,8

Further evidence that even a single borderline, or mild or moderately high blood pressure reading indicates the presence of hypertension was obtained by the writer who called back for re-examination fifty hospital patients 40 years of age and over because in their hospital stay, during routine examinations, only one blood pressure had been recorded. These were blood pressures only on the borderline of hypertension and the single readings were 152/80, 158/90, 150/80, 150/80, 150/90,

Age

40-49 50-59 60-69

40-49

50-59

60-69

| • | Men | | |
|---------|--------|--------|---------|
| 140/90† | 150/90 | 150/95 | 150/100 |
| 33.6% | 25.9% | 16.9% | 15.4% |
| 49.2% | 40.6% | 32.8% | 31.7% |
| 66.5% | 56.3% | 51.0% | 50.4% |

23.6%

46.6%

64.5%

22.7%

45.5%

64.0%

Table I
HYPERTENSION BY AGE*

Women

32.0%

53.4%

67.7%

39.2%

64.6%

77.9%

particularly unreliable since a hospital is supposed to place the patient under emotional and mental stress. Yet on re-examination of these fifty patients, I to 7 years later, with many blood pressure readings on each patient, 76 per cent were found to possess definite hypertension, usually much higher than the single initial reading previously obtained in the hospital and at least one-fourth disclosed a diastolic blood pressure over 100. The following are the respective readings: 125/80, 160/90, 150/95, 128/90, 150/95, 185/105, 168/95, 158/105, 145/82, 158/108, 170/105, 140/80, 185/90, 198/112, 160/86, 137/75, 170/95, 128/82, 154/76, 155/95, 165/100, 178/105, 160/96, 168/94, 155/90.

From this discussion it is clear that there are many important approaches to the question of hypertension in wartime. Not only may athletes be turned away if one strictly adheres to military standards for hypertension but also it may be impossible to obtain the 10 to 15 million men who may be under arms by the end of 1943.

Some new figures on the actual incidence of hypertension in people over 40 have a further and direct bearing on hypertension in wartime. 9,10,11,12 The following table is based on the blood pressure readings obtained from 15,000 men and women (Table II).

It is seen that on the basis of a systolic blood pressure 150 mm. or over, and/or diastolic 90 or over, a little over one-fourth of the men

[†] Cases are included if either the systolic or diastolic is within the specified limits.

TABLE II

ESTIMATED INCIDENCE OF HYPERTENSION OF VARIOUS DEGREES
AMONG WHITE PERSONS IN THE GENERAL POPULATION OVER AGE 40

| Degree of hypertension* (in mm.): Age group (years) | Percentage Male-Female | |
|--|---------------------------|--|
| 140/90 or over: | | |
| 40 and over | 49.8 59.8 | |
| 50 and over | 59.9 72.5 | |
| 20 7 | 70.5 79.6 | |
| 70 and over | 77.3 82.2 | |
| 150/90 or over: | | |
| 40 and over | 40.9 50.7 | |
| 50 and over | 50.3 - 62.2 | |
| 60 and over | 59.8 70.2 | |
| 70 and over | 65.8 74.0 | |

^{*} Cases are included if either the systolic or diastolic is within the specified limits

40 to 49 have hypertension; a little over two-fifths at 50 to 59 years; and considerably more than half at 60 to 69 years. Women have considerably higher figures. This is significant here because the Navy is accepting many women for certain types of service during the emergency.

Considering 140 and/or 90 or over, figures the insurance companies have shown to exert a definite effect on mortality rate, the incidence of hypertension is still higher. Just about one-third of the men between 40 and 49 years of age have hypertension, approximately one-half between 50 and 59, and two-thirds in the seventh decade! Again, women reveal a considerably higher frequency than men.

A study of these tables then reveals that hypertension is common in those over the age of forty. An even clearer exposition is presented when compilations based on the percentages in the tables just described and the distribution of the population¹³ are made (Table II). It is then obvious that among men 40 years of age and over, the incidence of blood pressure 140 plus and/or 90 plus would be 50 per cent; 50 years and over, 60 per cent; 60 years and over, 70.5 per cent; for women the figures are 60 per cent, 72.5 per cent, and 80 per cent respectively. For blood pressure limits of 150 plus and/or 90, the proportions for men

would be, for 40 years of age and over, 41 per cent; 50 years of age and over, 50 per cent; 60 years of age and over, 60 per cent; and for women, 51 per cent, 62 per cent, and 70 per cent respectively.

In other words, in the population 40 years of age and over, hypertension, as I have defined it, is so common that it can no longer be considered abnormal. If, then, these limits, and probably a little higher limits, are not abnormal it may indicate that our standards in the military forces are too high. Should they be lowered? Yet I have just shown that blood pressures around these limits at these ages and in younger ages may mean definite hypertension in later life. Before I answer these questions I wish to point out that I am making no statements about morbidity or mortality. I do believe that a group of men with a blood pressure of 110 systolic will, in general, live longer than another group, no matter whether 17 or 57, with a systolic blood pressure of 150 or 170 mm. Hg. Of course certain limits should always be considered abnormal, e. g., a diastolic of 110 or over (possibly 100 or over) and a systolic blood pressure of 200 or over (possibly even 190 or 180 mm. Hg.). The exact limits of "normal" blood pressure for the different ages is being worked out for us at the Statistical Bureau of the Metropolitan Life Insurance Company, New York City, by Mr. H. H. Marks.

To repeat, then, it appears that hypertension within the limits ordinarily accepted is so common that it may not be considered abnormal. On the other side of the picture is the observation on my tour in December 1942 of the U.S. Naval Hospitals at Oakland, Treasure Island, Marc Island, and San Diego, that among the "war casualties" were at least sixteen men between the ages 26 and 27 who came to my personal attention and who were being surveyed/or discharged with the diagnosis of arterial hypertension. Many broke down a few months after enlistment, one after only 29 days and another after only 2 months. The complaints were shortness of breath, dizziness, precordial pain and the blood pressures obtained were not infrequently high, for example: 156/110, 190/126, 180/86, 210/130, 178/114, 160/80, 160/104, 180/104, 170/104. Again and again the story was that of a borderline blood pressure reading on enlistment or re-enlistment. On the jacket of a 43 (P-S) year old man in the U. S. Naval Hospital at Oakland was this notation: "He had no knowledge of having an abnormal blood pressure until he tried to enlist in the U.S. Marine Corps Reserve at which time he finally passed this test after having to sit quietly in a chair for half an hour.

Three previous blood pressures that day had been unsatisfactory." He was finally taken in with a blood pressure of 150/90. His complaint was precordial pain on slight exertion.

At the U. S. Naval Hospital, Mare Island, a young Lieutenant (jg) age 34 (M.K.C.) was being surveyed for discharge after 5 months of active duty because his blood pressure was 190/126, yet he had been refused life insurance at the age of 19 because of elevated blood pressure!

A man of 26 (L.R.H.), at the U. S. Naval Hospital, Mare Island, California, after 4 months service complained of dizziness and shortness of breath on board ship. His blood pressure was 188/86. Investigation showed that he had been rechecked and rechecked for his blood pressure at enlistment and finally it was recorded as 140/78. It was found that 3 years prior to enlistment he had visited a physician because of dizziness, shortness of breath and blurring of vision. He, like the preceding men with hypertension, probably had definite organic cardiovascular disease.

A private in the U. S. Marine Corps (R.C.B.), 22 years of age, was being discharged at the U. S. Naval Hospital, Mare Island, only 4 months after enlistment, because of high blood pressure readings, 160/80, 150 85, and complaints of dizziness and shortness of breath. His story showed that 6 months prior to enlistment he had been rejected by the Navy because of high blood pressure, and on this hospital admission actual valvular heart disease was found, again revealing organic heart disease as well as hypertension.

Some of these men with hypertension broke down at training camps, or on board ship. A man (L.E.) 22 years of age broke down 29 days after enlistment when the work at the U. S. Naval Training Station at San Diego was too hard for him. On inquiry of his family physician, it was found that he had treated this apprentice seaman for 3 years because of hypertension.

R. W. B.. 38 years of age, machinist mate second class, complained of headache and dizziness while on board a destroyer. His blood pressure was found to be over 200 mm. systolic. He was hospitalized at the U. S. Naval Hospital. Oakland, California, November 30, 1942, and blood pressures of 170-190 systolic and 120-130 diasrolic were recorded. The electrocardiogram revealed evidence of myocardial involvement for the T-waves in leads I and IV were inverted. On the

hospital jacket was the interesting remark that at the time of enlistment the recruit had been examined and re-examined because of abnormally high blood pressure readings and finally "grudgingly accepted for enlistment August 21, 1942." It is thus a case in which high blood pressure readings came down to normal or borderline figures after rest and repeated examinations. Had he had a complete examination including fluoroscopy and electrocardiogram at the time of enlistment, I am confident evidence of organic heart disease would have been found. The very fact, too, that diastolic blood pressures as high as 120-130 mm. Hg. were obtained at the Oakland Hospital indicates that a considerable hypertension must have existed for many years before enlistment.

These histories could be multiplied. Whether they were young enlistees or men in their forties, recalled from retirement to take an active part in the war, the story was invariably of the difficulty of getting by on physical examination because of hypertension. Repeated examination at rest and zeal to get into the Navy were both factors in their final acceptance. It would seem that borderline blood pressure patients should be thoroughly examined for organic disease of the heart, blood vessels and kidneys, before they are accepted at all.

To recapitulate, there are so many arguments for and against accepting men in the Navy who possess borderline blood pressure readings that it would appear a difficult problem to settle. It has been shown that hypertension at the customary limits now accepted is common in certain ages which suggests that our standards may be too high at those ages. Again, we know that with slight or moderate hypertension a person is often of excellent physique, even athletic and would be valuable on task force duty for many years. Since the indication is, too, that millions of men and women will be required in the armed forces, our physical standards for enlistment must not be too high. Against these arguments for the acceptance of candidates for the Navy with borderline or slight hypertension are the facts that even a single hypertensive blood pressure reading may be significant of future hypertension, that many of these may already have cardiovascular disease and if accepted may become a burden to the government.

To clarify the issues and to summarize the arguments it seems clear that anyone with definite high blood pressure has no place in the Navy for general service and even a single diastolic reading beyond 100 to 110 mm. Hg. no matter what the subsequent readings, should disqualify

the man. Secondly, in every doubtful or borderline case a complete physical examination should be performed and if possible it should include x-ray film of the chest or fluoroscopy for heart size, electrocardiogram for myocardial involvement, standard exercise test and electrocardiogram after such exercise. The "2-step" is a good test for this purpose because the amount of exercise is graded according to age, weight and sex. 15-16 In other words, if there is any evidence of cardiac enlargement, myocardial involvement or coronary insufficiency, the patient should not be accepted. Incidentally, an examination of the fundus vessels should be routine.

Thirdly, it is suggested that condidates whose blood pressures are of the borderline type described be accepted in both the Regular Navy and the Reserve under waiver in time of emergency provided a law is enacted by the Congress that no compensation or pension be paid to such a person because of the appearance of a definite hypertension or an increase in blood pressure during such service. It is advisable that Congress do this immediately so that the Navy may obtain an adequate number of desirable men and to spare the government hundreds of millions of dollars in pensions for a condition which becomes apparent or progressive with age and which is not due to war service.*

The Navy should still exercise the right, during peace and war, to set its own limits. That the Navy has been wise to be strict in peace time can be confirmed by the fact that during a special examination of Naval officers between the ages of 58 and 64 in August 1942, the incidence of so-called borderline hypertension or actual hypertension was considerably less than in the general population.

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RUSSIAN PSYCHIATRY-ITS HISTORICAL AND IDEOLOGICAL BACKGROUND*

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The history of Russian culture cannot easily be understood unless one bears constantly in mind the special circumstances of its evolution. Russia is an old country, of course; she is rich in tradition and great events. But unlike the rest of Europe, she was never in intimate historical contact with the classical civilization of Greece and Rome, and the Byzantine influences came late and were more or less limited to the religious trends of the Eastern Church. Whatever streams of classical inheritance there were in Russia came via Western Europe, after Europe had already gone through the Middle Ages and the Renaissance and was approaching the French Revolution. Russia remained isolated for many centuries. When Ivan III, in 1480, threw off the yoke of the Mongolians who had overrun Russia, Europe was already at the great turn from medievalism to the Renaissance. When Rodrigo Borgia ascended the throne of St. Peter in 1492, the year America was discovered. Russia was still almost as isolated as China and had nothing to contribute to the Western World. Nor did she yet possess the curiosity and impulse to acquire and assimilate what Europe had to offer. When Galileo died and Newton was born in 1642, Francis Bacon had been dead for sixteen years and Shakespeare for twenty-six, but Russia was still deeply rooted in her own semi-Byzantine tradition, without a literature of her own, torn by civil strife, steeped in problems which were far from the scientific, artistic, and religious revolutions of Europe. Russia did not establish any definite cultural contact with Western Europe until the eighteenth century. The French Revolution was already in the making and a new economic class was about to enter the political scene of Europe: Russia was at the time still a vast feudal country with millions of serfs, an autocratic governing class, no middle class, and almost no industry.

The cultural contact with the Western World once established,

^{· 100} sere! Neversier 3, 1942 before The New York Society for Medical History.

Russia proved a capable and original pupil. Within one century, or not very much more than that, she not only became a legitimate member of the European cultural family but succeeded in making great contributions to that culture. Dostoyevsky, Tolstoy, and Tschaikovsky belong to the whole world as well as to Russia; the work of Mendelyeev in chemistry, Bechterev in neurology, and Korsakov in psychiatry became an integral part of European science; as early as 1818 Lobachevsky's contributions testified to the maturity of Russian mathematical scholarship and its revolutionary approach to the revision of Euclidian geometry. Now, some one hundred and fifty years after the French Revolution, hardly a century and one-half after Russia joined the Western World, Russia stands politically, economically, and scientifically a full equal and in many respects a superior to the old Western European tradition. Such phenomenal assimilation of centuries of European culture could not help but produce certain unique paradoxes.

Through the channels of institutional religion, England, the oldest parliamentary country in the world, found herself on rather intimate terms with Imperial Russia, the oldest and the most absolute autocracy in Europe until 1917. For generations the Bishop of Canterbury felt spiritually at home in the Holy Synod of the Russian Church Orthodoxy. The Russian liberal, academic intellectuals espoused the cause of constitutional, parliamentary government in the English tradition, while Russian imperial policy stood out as the logical enemy of British imperialism.

The revolutionary forces of Russia, coming from the lower economic strata, espoused the most advanced European economic theories, those of Marxism; these theories were based on problems which arose in the most industrialized countries of Europe, while Russia remained primarily agrarian and almost feudal to the very last day of the Empire. The cultural varnish of the upper classes became French; the industrial trends were taken mostly from Germany and only recently from America; the scientific methodology was as much German as it was French. Philosophy and literature and music remained singularly Russian. In short, the picture of Russian culture is truly kaleidoscopic. The history of Russian medicine, and particularly of psychiatry, reflects both the meteoric rise of Russian science and those especially Russian peculiarities which were not lost in the process of rapid assimilation of forcign importations.

These Russian peculiarities could be summarized very briefly; any aspect of Russian cultural efforts is permeated with the spirit of high humanitarian social aspirations for reform combined with a spirit of revolutionary struggle against the bureaucracy and the autocratic cruelty and stupidity of Russian political and economic absolutism. It is this social motif that reverberates through every step of Russian medical history. This is no less true of psychiatry, the youngest of all medical specialties, one not yet wholeheartedly accepted even by the medicine of the Western World, Psychiatry has its own history, and because psychological problems are more intimately connected with the development of religions and philosophy, psychiatry was delayed and almost stunted in its growth all over the world. It first languished outside medicine and later lagged behind it. Only within our time has psychiatry established itself as a legitimate branch of medicine and as a discipline which has succeeded in building its own methodological foundation and in developing its own scientific procedure. Russian psychiatry, while no exception in this respect, had a longer and more arduous road to cover.

There was no inkling of psychiatry in Russia till the latter part of the eighteenth century. The first retreat for the mentally ill in St. Petersburg was opened as late as 1779. France at that time already had a detailed classification of mental diseases produced by Boissier de Sauvages. Young Philippe Pinel, who was to revolutionize the care of the mentally ill, was already in Paris. Mesmer was known in Paris as well as in Vienna. How small and insignificant the retreat in St. Petersburg was one may deduce from the fact that five years after its opening it had but thirty-two rooms; in another five years-in the year the first shot of the French Revolution was fired-the number of rooms was increased to forty, ten of which were reserved for more affluent patients. By way of contrast, let us recall that there was a hospital for the mentally ill in Cairo five hundred years earlier. There was one in Valencia at the beginning of the fourteenth century. There was one in Saragora around 1425, in Toledo in 1483, in Madrid in 1540, in Stockholm in 1551, and in Zürich in 1570. Bedlam was already an ancient institution in 1779. The York Lunatic Asylum was opened in 1777-it was three stories high and accommodated one hundred and eighty patients.

There were many mentally ill in Ruccia, of course. They wandered about in the streets and in the woods and some of them were taken

care of by the monasteries. But in one respect, Russia stands out as a happy exception in the otherwise gruesome history of psychiatry the world over. The European tradition of burning the mentally ill as witches did not develop independently in Russia, nor was it imported into Russia from Western Europe. Not being influenced by the Roman Catholic Church, Russian Church Orthodoxy, which has such a bloody and dark record in the political history of Russia, did not couple mental disease with Lucifer and produced no special theological psychiatry, nor did it have an Inquisition to raise the heated quarrels with the medical profession. The idea, if not the concept, that mental diseases are real diseases seems to have been established toward the beginning of the eighteenth century in Russia.

The following incident occurred in 1701. A psychotic by the name of Nikonov wandered among some guards who were on duty and told them the Tsar should be cursed because he had introduced into the Moscovite Tsardom such innovations as "German" stockings and shoes. Nikonov was arrested. An investigation was started but the offender could not be examined properly: "He screamed and threw himself about and used unintelligible words and spat on the image of the Holy Virgin. He was chained and held to a heavy trunk by three soldiers, but he broke away, fell to the floor, and snorted loudly for a long time; while doing so he fell asleep. The investigators concluded that the man was crazy and suffered from falling sickness." No mention was made in the report of any attending physician. On April 28, 1701, the Tsar himself issued a ukase to the effect that the miscreant be sent to a monastery for a month's observation in order to establish "what sickness and craze he may reveal." A month later the monastery reported that "no sickness or craze was found, that the man spoke no foolish words, and that he was on the whole in possession of his mind and reason." Thereupon the Tsar ordered that Nikonov, "in consequence of his misdemeanor and indecent language, be punished with a whip, then branded, and exiled to Siberia for life with his wife and children."1

Peter the Great evidently understood the medicopsychological inadequacy of monasteries, and as early as 1723 he formally forbade sending the mentally ill to monasteries and ordered the construction of mental hospitals. But even the power of a despotic Tsar cannot overcome the inertia of his own bureaucracy or that of a historical tradition. Nothing

U. Kannabich, History of Psychiatry (in Russian). State Publishing House, 1928.

was done. Almost forty years later, in 1762, the Senate ordered specifically that the psychotic prince Kozlovski "should not be sent to a monastery but to a special house which is to be built for this purpose, as is the custom in foreign lands, where they have established dollhouses—so be it."

The origin of the term "dollhouse" is not clear. It is used frequently in the Russian psychiatric literature of the eighteenth and of the first part of the nineteenth century. It is apparently a perversion of the German *Tollhaus*, house for the insane.

There was no Russian physician at that time who could advise how to build a "dollhouse" in accordance with "the custom in foreign lands." The Senate inquired of the Academy of Sciences and a historiographer by the name of Muler provided the authorities with a brief description of what a "dollhouse" should be and what kinds of insane people there are. He recommended that a doctor be put in charge of such a house, and he stated definitely that the business of treating the mentally ill should be left in the hands of the physician. The priest, he said, had nothing to do with insane people until they come to their senses and regain their reason.

However, some years passed before finally the "yellow house," as they began to be called, opened. In 1766 an order was issued in St. Petersburg demanding that anyone who knew of or gave refuge to a mentally ill person should report the latter to the police. The police were very soon overwhelmed with reports. In 1776 a small "yellow house" was opened in Novgorod, and another in Moscow. As has been mentioned already, the capital of Russia did not have one until 1770. All were founded in the close neighborhood of monasteries and most even carried the names of the latter.

From this time on a series of hospitals opened all over Russia. In 1814 they were put under the supervision of a department of the Ministry of the Interior. By 1860 there were forty-three hospitals for the mentally ill in Russia—all small, all inadequately run, and all governed in the tradition of cruelty. The cautery, whips, chains, so-called "isolators"—more or less Russian editions of the European padded cells—were all used freely in the management of patients. In 1820 the Moscow "dollhouse" had twenty-five sets of chains for one hundred and thirteen patients.

² Ibid

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The years during and following the Napoleonic Wars brought Russia closer to European political thought and European scholarship. But the brief honeymoon of the sentimental liberalism of Alexander I ended in disappointment for those whose liberal hopes outlived the youthful impulses of the Russian Emperor. The Decembrist rebellion in 1825 ended with the complete triumph of autocracy. The reign of Nicholas I started with blood and continued in an atmosphere of darkest reaction. In the meantime, Russian economic life underwent the gradual but definite change which had characterized Europe two full generations earlier. A commercial and industrial class developed which was unable to make peace with the selfish, autocratic rule of Tsardom or to support the ruinous tradition of serfdom on which the ruling classes of the Russian Empire had fattened. The opposition of the newly born class served only to intensify the iron rule of autocracy. The country's needs grew; problems of public health, of building new hospitals, of caring for the mentally ill were all concentrated in the hands of a dull, complacent, and self-contained bureaucracy to which a well-organized secret police system was of greater value than measures of social welfare. Under the circumstances, psychiatry did not have the necessary opportunity to develop. Mental patients were not only treated with cruelty but even their most elementary needs were not provided for. They were fed atrociously, meat being served at only rare intervals; laundry was not provided; filth, hunger, and cruelty summarize briefly but poignantly the status of the mentally ill. In the words of a contemporary writer, the mental hospitals were "a branch of Dante's Inferno."

However, the fermentation of newer forces in Russia, once started, would not stop. Russian autocracy was forced to abolish serfdom in 1861, and by 1867 Russian bureaucracy had to yield a little more ground. It transferred the supervision of mental hospitals to the "zemstvos"-the semi-official, civic organizations which represented the major strivings of the new "third estate" for rational public welfare. Permission was given to the zemstvos and even to certain municipalities to build new hospitals. The need for physicians and surgeons was acute; greater still was the need for physicians trained in psychiatry.

The early 'sixties of the past century marked the true beginnings of

Russian psychiatry. In 1862 the short-lived "Society of Physicians for the Insane" was organized. This was the parent of the Petersburg Society of Psychiatrists, which was founded in 1880. How slowly psychiatry grew in Russia may be judged from the fact that out of the four hundred and forty physicians who attended the first all-Russian psychiatric meeting at Moscow, in January 1887, there were only eighty-six who specialized in the study and treatment of mental diseases. The very small number of psychiatrists was due not to the lack of interest. This interest was very great indeed, but there were no well-organized institutions where one could learn clinical psychiatry, nor was psychiatry taught in the medical schools.

It is easily seen that Russian psychiatry is hardly three-quarters of a century old, and that it began in an atmosphere of political strife, bureaucratic inefficiency, cultural darkness, and economic misery. The fact that within the short period of seventy to seventy-five years Russian neurology and psychiatry caught up with Europe and contributed to the world such men as Merjeyevski, Korsakov, Bechterev, and Pavlov testifies to the uniquely untiring and creative activity of Russian medical science, which found itself capable of overcoming the immense obstacles which the bleak autocratic regime, wars, and revolutions continually raised in its path.

The particular political and economic circumstances in which Russian psychiatry had to develop also determined its major trends. It was inspired with the ideal of building as many mental hospitals as possible, and of abolishing all forms of restraint. The nonrestraint movement inaugurated in England by Hill, Charlesworth, and Conolly, and associated primarily with the name of the latter, was a source of major inspiration to the Russians. The vicissitudes of this movement within Russia symbolized to a great extent the struggle for freedom which kept the country in a constant state of revolutionary fermentation till the end of the last War.

Next to nonrestraint and the creation of new hospitals, it was the education of the psychiatrist that stood in the foreground as a major problem. As to the scientific orientation of psychiatry, unlike Russia's literature and art or even some aspects of her political philosophy, it took a strictly materialistic turn rather narrowly conceived as neurobiological. The new contact with scientific Europe fascinated the Russian scholar, who sensed in it the rationalism and freedom of thought which

he craved so much and which stood in such contradiction to the superstitious and bigoted tradition inculcated into Russian life by Russian Church Orthodoxy and the political autocracy which used the latter as its tool. Biological materialsm was in great vogue in the 'sixties. The most popular book was Büchner's Stoff und Kraft, which became a sort of guidebook and passport for scientific respectability. Turgeniev described this trend beautifully in his Fathers and Sons. His Bazarov, the young physician who finally died of septicemia contracted at an autopsy, was typical of the time. He treated the idealistic fathers who still enjoyed playing 'cello music with a cold sneer and reproach. There was work to be done, there were things to be learned, there was a service to be rendered to the community, and all this musical sentimentality and leisurely romanticism had to be shed with scorn and determination. Since frogs were experimental animals, they were more valuable and therefore more important than a Beethoven. Even in his terminal delirium, Bazarov was preoccupied with dogs and not with mystical hallucinations.

Russian psychiatry, born at that period, established itself on a purely somatic and neurological basis. The first Russian professor of psychiatry was the pioneer, Balinsky. Balinsky graduated in medicine in 1856 and started specializing in pediatrics, which he soon abandoned. He went abroad to study and returned in 1867, in the same year the mental hospitals were turned over to the zemstvos. He took charge of the frightful psychiatric division of the Military Medical Academy, devoted himself to its reorganization, and made it a real hospital. He gave an immense amount of energy to the supervision of various projects for new mental hospitals all over European Russia. Balinsky was so busy with problems of psychiatric organization that he never had time to make any written contribution to psychiatry, and he always regretted it. Though he had no time for scientific research, he was an excellent, intuitive clinician. His influence as an inspired and inspiring teacher was incalculable.

Balinsky's somewhat younger contemporary and pupil, Merjeyevski, succeeded him as professor in 1877. Merjeyevski, rightly recognized as the father and dean of Russian psychiatry, was a great teacher and organizer. He trained more than fifty psychiatrists, eleven of whom taught psychiatry and occupied chairs of neurology and psychiatry. Twenty-six doctor's theses dealing with psychiatric subjects and one hundred and fifty scientific papers were written and published under his direction.

But unlike his predecessor Balinsky, Merjeyevski found time not only for teaching and organization but also for scientific research. He was in contact with European psychiatrists, particularly the French. His first study dealt with microcephalics; in this he tried to refute the new Darwinian hypothesis represented by Fogt which suggested that the brains of microcephalic individuals are related to those of anthropoid apes. Merjeyevski advanced the very keen and fruitful suggestion that the microcephalic brain was embryonic in nature. In 1872, jointly with Magnan, he made a study on the brain ventricles in general paralysis. In 1874, at the International Congress at Norwich. Merjeyevski described independently the giant pyramidal cells which became known as the cells of Betz, who was also a Russian neurologist, from Kiev. Merjevevski was president of the first Congress of Russian Psychiatrists in 1887 and held the chair of psychiatry until 1893. He was the founder of a tradition which later became known as the Petrograd School and, since the Revolution, as the Leningrad School of Psychiatry. This school was later headed by V. M. Bechterev (1857-1927), who also became the occupant of Merjeyevski's chair of psychiatry in the Military Medical Academy.

In a brief review such as the present one, it is impossible to do justice to the many important features of Russian psychiatric history or even to mention all its worthy representatives. P. I. Kovaevsky was the first to establish psychiatry in the south of Russia, in the University of Kharkov. Bechterev established it in the University of Kazan, and Kojevnikov in Moscow. The University of Dorpat, being directly under the cultural influence of Germany, as was all the Baltic region of Russia, was led by German professors. Emminghaus, from Freiburg, occupied the chair of psychiatry at Dorpat from 1880 to 1886, and for four years. from 1886 to 1890, Kraepelin was the incumbent. Yet on the whole Russian psychiatry was more under the influence of French than of German psychiatry. Even in later years, when the influence of Kraepelin's nosology spread all over the world, there was opposition to Kraepelin in Russia. Serbsky, the successor of Korsakov in Moscow, was not alone in objecting to Kraepelin's suggestion that the major psychoses should be diagnosed on the basis of their ultimate outcome. on the basis of what would happen to a given patient in the future. When Kraepelin claimed that dementia praecox could be recognized by the fact that it usually ends in mental deterioration, he himself admitted that about thirteen per cent of dementia praecox patients do recover. Serbsky is said to have observed, not without caustic wonderment, "Those patients, then, are dementias which do not end in dementias?" He considered the Kraepelinian diagnostic suggestions not a little puzzling.

It was French psychiatry with its succinct logic and clarity of description that seemed to appeal more to the Russian psychiatrists. They stood closer to Morel, Magnan, Charcot, and Janet. That Merjeyevski published a joint paper with Magnan has been mentioned. Korsakov's meticulous neuropsychiatry was certainly reminiscent of the methods of Magnan and Charcot, and Bechterev's work was definitely in the tradition of Charcot and Pierre Janet.

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By 1893, when Merjeyevski retired from active work, Russian psychiatry had established itself as far as its clinical and scientific methodology was concerned; it had also become a specialty, and it was represented by a number of well-trained and brilliant men. While Merjeyevski was laying the foundation of the Petersburg School, Moscow was developing more or less independently. The Moscow School is closely identified with the name of S. S. Korsakov.

Korsakov was born in 1854. He was not seventeen years old when he entered the Medical School of the University of Moscow. At the age of twenty-one he was already a member of the staff of the Préobrajensky Hospital in Moscow, and soon afterwards he became assistant to Kojevnikov, the pioneer of Moscow psychiatry. There was no really well-organized mental hospital in Moscow, nor was there any separate chair of psychiatry. Kojevnikov started giving a theoretical course in mental disease in 1863. Theretofore neurology and psychiatry had been a part of general pathology.

Not until 1887 was a good psychiatric clinic opened in Moscow. This clinic was built with the money donated by a private citizen (V. A. Morozova) in 1882. Kojevnikov was its first director, Korsakov was its factual head. How exiguous was the equipment offered at that time to a young physician interested in psychiatry one could judge from Korsakov's own reminiscences. "When I finished my medical course," he relates, "I came to the Préobrajensky Hospital in Moscow to apply for a job as physician. The physician-in-chief, a psychiatrist who en-

joyed a well-deserved good reputation, said to me: 'You were taught very little psychiatry in medical school, were you not? I am sure you don't even know how to tie down an insane person.' My first lesson was that of tying down. It is difficult to believe this—yer it all happened so very recently."³

Korsakov devoted himself to the liberation of the mentally ill; to the abolition of all measures of restraint, to the organization of the colony method of management. Through his efforts the "isolators" were abolished in 1895 and transformed into apartments for young physicians or chemical laboratories. His ideal of a mental hospital was one made up of a series of homelike, small houses in which patients were treated as sick people, as human beings. He achieved a great part of his ideal in a small colony for the mentally ill near Moscow. It was a gigantic task to which Korsakov devoted his inspiration and energy. His pupil Serbsky called this achievement "Korsakov's scientific work which was never published anywhere."

In accordance with the tradition of Russian psychiatry, Korsakov's efforts were organizational and humanistic, but he found time for intensive clinical research. He left a complete and rather voluminous classification of mental diseases which demonstrates great powers of observation and rich clinical experience. While he was interested in all aspects of psychiatry, Korsakov's chief interests were concentrated on the neuropsychiatric aspects of alcoholism. The choice of this interest was not accidental. Russia offered unusual opportunities for the study of alcoholism. The Tsarist regime was one of the major factors in the development of alcoholism, for alcohol was a monopoly of the state, under the direction of the Ministry of Finance. The Tsarist treasury was regularly replenished at the expense of the population, which was given a liberal opportunity to develop alcoholic addiction. The stores selling vodka were known in Russia not as saloons, but as "monopolkas." The workingman would enter the government store, would buy a bottle of vodka duly sealed with the government sealing wax, uncork it in the street at the door of the monopolka, and drink it straight without food or chaser. Alcoholism in Tsarist Russia was as typical and chronic a disease as was Tsardom itself.

Heavy drinking was so much a part of Russian life that it is reflected in a legend, probably apocrypital, about the adoption of the Greek

^{*} Ibid.

Orthodox Christian faith by Russia. It was Prince Vladimir, later canonized by the Russian Church, who decided to espouse one of the monotheistic religions. He invited representatives of all existing religions; the Catholics, the Mohammedans, the Jews, and the Greek Orthodox sent delegates to bid Vladimir join their respective churches. Vladimir rejected the Catholics because a Russian prince, he averred, would pay no obeisance to anyone, even to the Prince of the Church. The Jews Vladimir rejected because their religion forbade eating pork. This was in the middle of the ninth century, and Russia was mostly what now is the Ukraine; the population raised a number of pigs, and Vladimir's rejection of the Mosaic religion seems to have been dictated by prudent economic considerations. The Mohammedans had even less to offer; on hearing that Mohammed forbade the use of intoxicating liquor, Vladimir is supposed to have become more explicit. "Russia," he claimed, "lives on the joy of drinking and cannot live without it." This reduced his choice to the Greek Orthodox Church, the tenets of which he accepted by mass baptism in 862. From that year on the Russian Tsars were devout rulers, ruling Russia and the obsequious church, which was an obedient servant of Tsardom and helpful in promulgating the theory of "the joy of drinking without which Russia could not live."

A little over one thousand years after the official consecration of Russian alcoholism, Korsakov made a studious examination of the clinical consequences of this legendary choice. It was at the first Congress of Russian Psychiatrists, which opened in Moscow on January 5, 1887, that Korsakov presented his first studies. The president of the Congress, Merjeyevski, reflected in his opening address the deep concern of Russian psychiatry—a concern which found its practical and creative expression only after the Soviet Revolution. The topic of the address was "The conditions which are conducive to the development of mental diseases in Russia, and the measures necessary for their prevention." Korsakov read two papers, one on the care of the mentally sick in private homes and the other on nonrestraint. Thus we may see that the sociological orientation of Russian psychiatry and its civic conscience came to full expression at that early date.

In the very same year, Korsakov submitted his thesis "On Alcoholic Paralysis." Two years later he published a paper entitled, "Some cases of a singular cerebropathy combined with polyneuritis." He worked out in detail not only the neurological picture of the alcoholic psychosis.

but also the psychological one—the typical memory disturbances, the characteristic, retrospective pseudologias and fabrications.

Korsakov was a quiet, unassuming, modest worker; he even gave the impression of being insecure. His was the true attitude of a scientist in whom modesty and greatness were perfectly integrated. At the International Congress of Medicine in Paris, in 1900, Professor M. Ritti. speaking in memory of Korsakov, recalled: "It was at the International Congress in 1889. I remember vividly how Korsakov came over to me modestly, almost timidly; his characteristic face reflected a vital, keen mind. goodness and endless gentleness. His was the nature of an apostle and of a scientist. He had in his hands a manuscript and asked my permission to present it; it was not scheduled on the program. I was glad to give him permission. You all know the monumental contribution which this happened to be, a contribution which opened a new era in our science. It was entitled simply: 'A form of mental disease which is combined with degenerative polyneuritis.' The paper was received with warmest applause. The great scientist who presided over that meeting was Professor Benedict of Vienna. This man of vast knowledge and incontestable competence evaluated that highly original paper with the following words: 'We thank Doctor Korsakov for his interesting paper. He has confirmed to the highest degree the theory that all psychopathology can be reduced to lesions of the brain and nerve-tissue in general.' "

As we know now, Benedict's hopes were too expansive, although they are still cherished by many today. Benedict's at the time more obscure colleague and compatriot, Sigmund Freud, was already back from Paris where he had worked with Charcot, and together with Joseph Breuer he was initiating an even greater revolution in psychopathology than was Korsakov's in the consideration of alcoholic reactions. This is noted, not to deter from the greatness of Korsakov, but rather to emphasize the fact that while European psychiatry was studying hysteria, revealing a new insight into neuroses, and preparing a new theory of psychopathology, Russian psychiatry seemed in a strange way to neglect the whole field of neuroses and to concentrate on the neuropathological conditions which were brought into focus by the special social and cultural circumstances in which Russia lived.

At the International Congress of Medicine held in Moscow in 1897, the Berlin neurologist Jolly proposed that the alcoholic psychosis de-

scribed by Korsakov be called the Korsakov Psychosis, which is the official term used in all psychiatric classifications today.

Korsakov's career left an indelible imprint on the history of Russian psychiatry, and the period in which he lived and wrote is known as the "era of Korsakov." Korsakov died on May first, 1900, closing less than half a century of exceptionally eventful psychiatric history.

IV

The twentieth century opened rather inauspiciously. The Russo-Japanese War, the tempestuous revolutionary upheavals, the famines and the persecutions on the part of the Tsarist regime hampered Russian culture and Russian science, disturbed and disrupted Russian life, till finally the structure of Tsarist Russia crumbled, as one day it had to, in March and November, 1917.

The special conditions of Russian political and social history only enhanced the scientific and cultural orientation of Russian psychiatry. As everywhere else in Europe throughout the nineteenth century, psychiatry was not psychological but administrative, custodial, descriptive, and neurological. The deep-seated human psychological conflicts, the inner tragedies of man's relation to himself and to the outside world, were still as if by general, silent consent considered as belonging more to literature than to psychiatry. The psychological aspects of psychiatry were left in Russia to Dostoyevsky as much as they were left in France to Hugo, Dumas the younger, Maupassant, and Proust, or in Sweden to Strindberg, or in Norway to Hamsun. The old, mistaken view that psychiatry, in order to be scientific, must be objective-that is, must leave the subjective states, the ideational content, out of consideration in favor of their neurophysiological equivalents-prevailed in Russia perhaps to a greater degree than in the rest of Europe. The term "neuropsychiatry," which is more or less new in English speaking countries, is an old term in Russia.

The twentieth century is marked by the development of what has become known as objective psychology, or reflexology. These terms were introduced by Bechterev. The history of this period is too recent, and a proper historical evaluation of it is not yet timely. Suffice it to say that already there are signs of considerable distortion of the historical perspective regarding the recent trends of Russian psychiatry, and an attempt to correct this distortion may not be out of place.

The reflexological ideas in psychiatry are not very recent. Almost one hundred years ago Griesinger spoke of "the reflexes of the brain," and in 1863 the Russian neurologist Syechenov published a monumental work entitled, The Reflexes of the Brain. The work of I. P. Pavlov was purely physiological, and for a long time Pavlov failed to deal with the possible psychological implications of his experiments. He never actually worked on human beings, and he never subjected the variety of emotional subjective states of human beings to experimental evaluation. Having been a direct witness of this page of Russian psychiatric history, I may be permitted to testify that the first reflexological experiments on human beings were made by Bechterev in the Psycho-Neurological Institute in Petrograd as early as 1912, and at that time Bechterev was already giving a course on "Objective Psychology or Reflexology." His Objective Psychology, in three volumes, was published between 1907 and 1912 and was translated into French and German. His Foundation of Reflexology of Man was published in 1918, and his Collective Reflexology in 1921. All these contributions were for some reason overlooked both in America and in England.

Pavlov's great contribution to the subject of conditioned reflexes remained outside medical psychology, and the recent theoretical constructions of what has become prematurely known as Pavlov's School do not go beyond a general neurophysiological theory. The so-called "experimental neuroses" in animals do not offer any conclusive results, in so far as the behavior of these "neurotic" animals is interpreted by the experimenter on the basis of his subjective impressions only. There is no proof that the animals actually labor under the stress of a psychological conflict. On the other hand, the method of Bechterev, while still more related to behaviorism than to true analytical psychology, nevertheless deals directly with human beings and therefore represents actual psychiatric work.

The last twenty-five years, the most interesting and valuable in the history of Russian medicine, mark more poignantly than ever before the sociological and neurophysiological orientation of Russian psychiatry. Since the Soviet Revolution, psychiatry has become a branch of public health when it is not a field of laboratory research. What is known here as "mental hygiene" has become the chief field of Russian psychiatric endeavor. Numerous clinics in municipalities and in industrial centers have been opened, and the whole working population is

brought into the orbit of psychological supervision and educational efforts. Psychiatry, to use the words of the great leader of Soviet psychiatry, L. M. Rosenstein, has become a system for "the protection of neuropsychic health." Sanatoria for borderline cases and for neuroses have been organized. These are psychotherapeutic and physicotherapeutic centers. Social hygiene and prophylaxis are the guiding principles.

The accent is on purely cultural factors. As the Russian historian of psychiatry, Kannabich, summarizes it briefly, "The study of the cultural conditions and of the influence of environment, the concentration of special attention on the role of social factors and psychogenic moments, leads more and more to the rejection of the endogenous and to the increasing acceptance of the exogenous forms" in the consideration of psychopathological reactions.

LIMITATIONS OF PSYCHOANALYTIC TREATMENT*

HERMAN NUNBERG

one expects that all patients who are treated by physicians are to be completely cured. A complete restoration to normalcy, however, seems to be expected from psychoanalysis.

What is psychic normalcy? Is it not a relative notion

What is psychic normalcy? Is it not a relative notion dependent on many factors? One patient may well be satisfied with the results of his analytic treatment while his family and his friends may be dissatisfied. Another patient may be dissatisfied, whereas his family and his friends may praise the results of his treatment.

A patient suffering from an incurable chronic organic disease is happy when he is sufficiently improved to carry on his work. The same applies to some psychoneurotics whose health has improved without complete recovery. Curiously enough, different standards are applied to the therapeutic results of the analyst than to those of other physicians. This, perhaps, is partly explained by the fact that for the outsider it is not so easy to determine whether a cure was successful or not. There occur, no doubt, failures in analyses and there is no reason why this should not be admitted. In order to promote a better understanding between analyst and non-analyst, I believe it advisable to discuss, though only superficially, the determining factors for some failures of psychoanalytic treatment.

I cannot fully discuss, in this presentation, the clinical indications and prognosis of the psychoanalytic treatment. Not only the non-analyst cannot decide whether a patient is suitable for analysis but also the analyst frequently has to postpone judgment until several months of analysis have elapsed. I would, therefore, prefer to discuss the difficulties from the analyst's viewpoint; in a sense, I would like to invite you to look into the analytic workshop.

All psychoneurotics suffer from an inner conflict. Hence the first

^{*} Paper read before the combined meeting of the Section of Neurology and Psychiatry of The New York Academy of Medicine and the New York Neurological Society, November 10th, 1942.

task of the treatment seems to be to relieve the patient of this conflict. Simple as this may seem, yet it is not so easily fulfilled. We cannot solve all conflicts and when we succeed in solving one conflict, we are not assured against the development of another in the future, just as we are not certain that an organic disease, once cured, may not recur.

The first difficulty in attempting to solve the neurotic conflict is that many patients do not even know that they have a conflict. The conflict is unconscious to them and the task of the analyst is to bring this conflict into the open, to make it conscious. In order to render a patient accessible to analytic treatment, he must at least be made aware of having a conflict; moreover, he must suffer. Patients who do not get this insight and who do not suffer will soon leave the analysis. The wish to be relieved from suffering drives the patient into analysis. Yet, if the analysis is to be brought to a successful conclusion, he has to be able to endure a certain amount of suffering during this period.

In order to understand this we should bear in mind that the neurotic symptom represents a compromise between self-denial of an instinctual demand and its gratification. The patient cannot, at the same time, enjoy the gratification and analyze it. The treatment, therefore must be carried out while the patient is frustrated by preventing the gratification of the particular instinct represented in the symptom. Some patients can endure these frustrations; others not, and then the analysis fails.

It is an accepted fact that a physically ill patient is endeavoring to help the doctor in all possible ways. In analysis, we are confronted with a paradoxical situation. Although the patient wants to be cured, at the same time he resists the treatment. As a rule, with the improvement of the patient's health and the favorable development of the analysis the opposition to the treatment becomes greater. Such a phenomenon, in general, does not appear in organic diseases and if it does, we know that the patient is psychically abnormal.

The opposition developed by the patient during his treatment is called resistance. Success or failure of the treatment depends largely on the nature of the resistances.

The psychoanalytic treatment, as is well known, is based on a sort of agreement between patient and analyst in which the analyst promises to try to help the patient to overcome his neurotic difficulties and the patient promises to confide all his thoughts to his analyst. All patients break this contract at various points of their analysis and develop resist-

ances which, in some cases, become insurmountable.

What are the causes of these resistances which become sometimes so powerful that they may even imperil the cure?

Instead of complicated theoretical explanations let me give a short

example:

A very intelligent and honest man wished to be cured of his depression. Long before he actually came to analysis, his wife and his friends had urged him to be analyzed but he had persistently refused. When he finally decided to be treated, his wife left him. The beginning of his analysis thus coincided with the separation from his wife. Soon after the treatment had started, he felt better. When he ascribed this improvement to the analysis, I remarked that it was too early to expect any results and that, in my opinion, his improvement was rather due to the separation from his wife. He did not agree with me and argued that he still loved her. At the same time, he began to produce more and more dreams which betrayed his latent homosexuality. When I called his attention to the fact that his latent homosexuality was striving for an outlet in his numerous dreams, he became indignant and said, more or less, the following: "Yes, perhaps this or that experience in my life, (which he had brought forth as associations to his dreams) may seem to support your interpretation, but the fact that I do not feel that I have homosexual trends, and never did, is more important than anything else. I cannot accept your interpretation." Since then he developed an utterly sriff resistance and it was impossible to penetrate much deeper.

It is obvious that this resistance was aimed at keeping the patient's homosexual strivings at an unconscious level. But why can the patient not accept his homosexuality, why has he to fight his analyst? Is he afraid of his own instincts? Yes, the ego of all patients is afraid of certain instincts. What compels the ego to fear its own instincts?

In real life, we become frightened when we are confronted with a danger; in other words, we get scared when we feel too weak to cope with an approaching menace. The ego of the neurotic person is weak and reacts therefore to danger with anxiety. The source of this danger, however, is not located in the outside world but within the patient, namely in his instincts. A weak person in real life is helpless and, consequently, does not fight but tries to escape the danger. The weak ego of the neurotic also strives to get away from his inner danger, instinctual demands. One cannot, however, run away from oneself. What one can

do, is to try to push the instincts away, to shut the eyes and cars to their urges, to withdraw one's attention from them. As a result, the ego does not know anything about their existence and its conflicts connected with them. This method of escape we call *repression*. Through this process of self-defense a previously weak ego becomes weaker; it becomes deaf, blind, mute and in many respects inhibited.

If you intend to strengthen a weak person in his combat against a danger, you equip him with better weapons, you train him in their use and encourage him to face the enemy. You cannot fight an invisible enemy and finally defeat him. In principle, the psychoanalyst does the same when he helps the neurotic to cope with his repressed instincts. He fortifies, strengthens the patient's ego by helping him to discover the unknown field of his unconscious, he encourages him to face the supposed dangers within himself, to criticize and reclassify them. Through this readjustment of the ego's attitude towards its instinctual demands, the ego becomes less strained, less tense and restricted, more independent in its judgment and freed of those inhibitions which previously limited its psychic activities to a considerable extent. The ego not only becomes stronger, but a balance is established between the energy of the ego and the energy of the instincts, a balance which, at any moment, can again be upset.

As mentioned before, not all patients respond favorably to the influence of the analyst.

A person's ability to socialize is one of the few essential conditions for his accessibility to any influence by others. In the psychoanalytic situation this ability forms the background for the transference, that is, a sort of unconscious shifting of the emotional attachments from father and mother to the analyst. A partial or complete loss of the ability to transfer emotions renders the analysis either very hard or impossible. That is the case with extreme narcissists and psychotics.

The transference can be a positive or a negative one; the basic attitude of the patient to his parents, which he shifts to the analyst, can be either love or hate. Usually both these feelings are mixed. As long as the positive feelings prevail, the analysis takes a smooth course. It happens, however, that the positive transference becomes too strong and the patient asks from his analyst real signs of attachment, of love, etc. As mentioned before, the analysis has to be carried out while the patient is frustrated and therefore the analyst must abstain from giving the patient

any gratification he may wish or demand from him. As a consequence, the patient is disappointed and soon the negative transference sets in. The patient starts to fight and spite the analyst, to hate him. In extreme cases the patient breaks off the treatment and blames the analysis for the failure. Thus the transference which is essential for the treament, under certain conditions, can become a source of resistances.

However, these resistances can mostly be mastered if carefully and patiently dealt with. Somewhat more difficult to overcome are other resistances.

As already mentioned, the ego of the neurotic is weak. The main manifestation of its weakness, perhaps, is its diminished capacity to harmonize psychic processes, in other words, to mediate between the demands of reality, the urges of the instincts and the moral standards of the ego.

If the ego is too weak to cope with the demands of the instincts, it undertakes a certain act which we have already mentioned as repression. This repression, once performed, is, however, not sufficient to check the instincts permanently. Therefore, the ego invents new methods of defense to reinforce them. These form often permanent character traits and habits. Let me illustrate this.

A patient seemed very modest, unassuming, retiring. Though actually brilliant, he felt inferior and was afraid to deal personally with anyone who seemed to be superior to him. Since he feared to make an unfavorable impression, he avoided being the center of attention in any gathering. He preferred to manage his affairs from the seclusion of his office room. Whenever his personal appearance in public was essential, he would send substitutes.

The analysis showed him gradually that, at the bottom, he was by no means so modest, but that on the contrary he was a very ambitious exhibitionist who indulged in elaborate phantasies about enormous successes, about being admired and honored as a hero. When this war broke out, this modest man could hardly resist the temptation to apply for a commission in the army, solely because of the glamour of the officer's uniform.

The childhood history revealed that, at this period, he derived great satisfaction from exposing his body, particularly his genitalia. Of course, he could not do that for a long time and was forced to repress this kind of gratification. But to maintain the repression was difficult, the pressure

of the frustrated instinct was too strong. So in puberty, there occurred a transformation in his ego: instead of indulging in various kinds of exhibitionistic gratification he became the modest, shy, withdrawn young man whom everybody found very pleasant to deal with. With this change in his behavior he developed a character trait which protected him permanently against a certain instinctual drive which, unchecked, would have been a source of conflicts.

There would be no objection to this solution of the conflict, if it did not result in great restrictions of the ego and subsequently in a very serious impairment of its activities. These restrictions and inhibitions, however, cause less discomfort than the constant struggle with the inadmissible instincts. Originally they are defenses, that is, reactions to the pressure of the repressed instincts. Later on they become fixated and stabilized in form of habits and character traits. They are, in fact, infantile ways of reactions of the ego to badly repressed instincts. When the attempt is being made to lift the repressions in analysis, which is always unpleasant to the patient, the old ways of reactions of the ego to the onrush of the instincts flare up very sharply and take, this time, the shape of resistance against the treatment. The old struggle of the patient's ego against the instincts changes now into the struggle of his personality with the analyst.

The outcome of this struggle depends on many factors. The resistances which the patients offer to the treatment may be easily overcome if the character traits are acquired, as a reaction to a trauma, caused, for instance, by an accident, frustration, loss of love, physical illness, etc. The problem is more difficult if the character traits have a constitutional background.

Each ego has, constitutionally, its own way of reacting. One person may be inclined to react vigorously, another one softly, one with projections, the other with identifications, etc. These reactions may form a weak spot in the development of the ego. They tend to repeat themselves, even in situations where other reactions would be more adequate. These inadequate reactions persist as peculiar traits of character. A neurosis expressed mainly in peculiarities of behavior is called character neurosis. In analysis, these peculiarities form very strong resistances and are very difficult to overcome. Even if the analyst succeeds in changing some of these character traits, the patient frequently relapses and repeats the old reactions and habits, though in a somewhat softened and dis-

guised form. The analyst has to try again and again to show the patient their origin and meaning. Therefore, the analysis of these cases may last for years, endlessly. And yet, this sacrifice on the part of patient and analyst is rewarded by the fact that the patient is being helped. This is not very different from the treatment in some organic diseases; a cardiac patient, for instance, has to be under his physician's care throughout his life.

The resistances against the cure due to the peculiarities of character, however, are not the ones that present the greatest difficulties. The resistances offered by that part of the ego that controls our moral ideals and is called conscience, rather, superego, are worse. Fulfillment of these ideals affords a specific pleasure. An attitude conflicting with these ideals causes a specific unpleasurable tension. This tension we call feeling of guilt, a term sometimes synonymously used with the term "need for punishment." I cannot go into details. I must, though, mention that conscience with its feeling of guilt is largely responsible for our social behavior, that it helps to subdue our most rebellious instincts, the sex instincts, our aggressions, etc. In as much as it contributes to check these instincts, it is indispensable. An oversensitive conscience, however, renders the individual unhappy, makes him suffer from sins which he did not commit, but which he may have fleetingly wished. Certain patients with an exaggerated feeling of guilt may go through an excellent analysis, may acquire insight into the dynamics of their repressed wishes and ideas and yet may not be cured. They feel unworthy of happiness, they rather enjoy constant repentance as a means of expiation. It is striking how submissive to their fate they are. Another characteristic fact is that an organic disease or a serious misfortune frequently relieves them from their neurotic sufferings.

Not even the feeling of guilt, however, is the most serious obstacle to recovery. There are types of patients whose every thought, idea, emotion, wish and action is accompanied by inner conflicts. I do not mean the ambivalence of the obsessional neurotic alone. In extreme cases it appears that everything patients of this kind experience is a source of immeasurable suffering. Even in dreams they torment themselves. When they enjoy themselves, they suffer like masochists; when others are enjoying themselves and they do not share that feeling, they suffer again, because they do not enjoy themselves. This inclination to inner conflicts, this need to suffer, is in certain cases so strong that it leads to dis-

aster. The ego becomes so weak that it gives itself up and yields to the overpowering forces of self-destruction. The analyst is often as unable to prevent the course of events as the internist is in an incurable cancer case.

I must stress that feeling of guilt and inclination to conflicts are not identical, though they may occur together. Cases with an excessive feeling of guilt and a strong inclination to conflicts present the greatest and most serious difficulties in the work of the analyst.

All these resistances still do not exhaust the difficulties encountered in analysis. Since I cannot discuss all of them, I wish to refer now to homosexuality. As is well known, homosexuality plays an important part in the causation of the neurosis. Man is bisexual. Under normal conditions his homosexual trends are well under control. Where the homosexual trends are more powerful, the control is more difficult, the ego has to develop stronger defenses and the analysis encounters greater resistances. The analyst may point out to the male patient very obvious feminine strivings and to the female patient very obvious masculine strivings, and yet they may not be able to face them. It is not easy to determine the cause of this stubborn resistance—perhaps biology plays a decisive part. The fact remains that a number of analyses fail at this point.

Summing up, we see that all the limitations to the psychoanalytic treatment are due to a *relatively* weak ego. It may be an absolutely weak ego confronted with instincts of average strength or an average, normal ego confronted with excessively strong instincts or an exceedingly severe conscience.

It is obvious that the term "weak" or "strong" means certain quantities of psychic energy which we, unfortunately, cannot measure, only estimate, Freud says: "Quantitative disharmonies in the distribution of psychic energies are responsible for the inadequacies and sufferings of the neurotic."* Consequently, the treatment is an economic problem: we should either diminish the quantities of the instinctual energies or increase the quantities of the ego energies.

The instincts cannot be influenced in a direct way, they can be influenced only through the help of the ego.

The outcome of the psychoanalytic treatment will depend on the ability to strengthen the relatively weak ego, in other words, on the ability of the analysis to mobilize and release enough energy within the

^{*} Freud, S. Outline of psycho-analysis, Internot. J. Psycho-Analysis, 1940, 21:469.

ego to enable it to cope with the other forces of the personality. In the majority of cases analysis succeeds in this task, in some cases it does not.

For the non-analyst this statement may appear obscure. Let me,

therefore, illustrate it with a short example.

A patient, a musician, came to analysis because of anxieties and difficulties in the practice of his profession. I learned, in a late stage of the treatment, of a habit of his to wash his hands before touching his instrument. Hiding this from me had been one form of his resistances. All my attempts to analyze this habit were futile. Finally I asked him to refrain from his hand-washing for the time being, well aware that he would not be able to comply fully with my request. His attempts to refrain from the washing and his inability to do so, produced great conflicts in the patient, which, at times, threatened to terminate the analysis. Fortunately he was not discouraged. Whenever he broke his promise, he felt compelled to think about his habit. For a long time he was convinced that he washed his hands following the advice of a famous teacher. This was merely a rationalization. Gradually, however, new facts emerged. To discuss all the pertaining material would go far beyond the scope of this paper. I would like to give only one important step of his analysis. When he, once again, broke his resolution not to wash his hands compulsively, he became aggravated by his own weakness and asked himself why he could not check his habit. He found no answer but, instead, the following recollection came to his mind: Once, when he had felt unhappy, low, desperate and unclean after continuous masturbation he consulted a physician, who advised him to wash his back and genitalia with cold water. Soon afterwards, a teacher pointed out to him that he produced an off-tune, "unclean" note with his instrument. (The patient was brought up in Germany and in German an off-tune note is called an unclean note.) In the same hour he remembered another important fact. At about the age of fifteen he became extremely elated when a member of a very famous symphonic orchestra heard him play his instrument and praised him highly. A few months later he heard a rumor that this musician had developed a stroke and died because he had produced an off-tune, "unclean" note, while playing his instrument before an audience. Many years later, when told by his teacher that he produced an "unclean" note, the musician's death came to his mind and he became frightened.

Not until the hour when this material came to the surface did the

patient see the connection between his masturbation and the fear of being punished for it, nor did he recognize that these were reflected in his attitude to his instrument.

This certainly does not exhaust the case, but let me stop here briefly and say the following: By encouraging the patient to refrain from the self-protection of washing his hands, the analyst helped him to face without fear the supposed dangers of masturbation and all wishes and ideas connected with it. Thus his ego became stronger in the combat against this infantile way of gratification.

This is an illustration, though incomplete, of the meaning of the words "mobilization of the energy of the ego."

Those who are not in sympathy with psychoanalysis will, most likely, derive great satisfaction from the fact that a representative of psychoanalysis admits publicly that psychoanalytic treatment can fail. Because of the human need for generalization they might add, I am afraid, analysis as a therapeutic method is of no value.

I can only say that I did not intend to talk about the successes of psychoanalysis; others have done that. What I intended to do was to try to explain from the dynamic viewpoint why certain failures in analysis are natural and cannot be avoided.

Let me close by quoting a few sentences from one of Freud's last works, published posthumously, words which are great in their simplicity:

"The future may teach us how to exercise direct influence, by means of particular chemical substances, upon the amounts of energy and their distribution in the apparatus of the mind. It may be that there are other undreamt of possibilities of therapy. But for the moment we have nothing better at our disposal than the technique of psychoanalysis, and for that reason, in spite of its limitations, it cannot be dismissed."

^{*} Freud, S. Outline of psycho analysis, Internat. J. Psycho-Analysis, 1940, 21:469.

THE VICAR OF WAKEFIELD BY DR. OLIVER GOLDSMITH A CHECK-LIST OF EDITIONS IN THE LESTA FORD CLAY COLLECTION IN THE LIBRARY OF THE NEW YORK ACADEMY OF MEDICINE

GERTRUDE L. ANNAN Rare Book Department

This collection was recently presented to the Library in memory of Dr. Linsly R. Williams, former Director of the Academy, by his daughter, Mrs. Lesta Ford Clay, who at one time was a member of the staff of the Rare Book Department. Goldsmith, remembered now for his writings, studied medicine at Edinburgh and is thought to have continued his studies during his travels on the continent. On his return to England he "set up as a physician in Bankside, Southwark," but was apparently unsuccessful in practice. His early connection with medicine, however, warrants the acceptance of this valuable and carefully compiled collection.

The most valuable editions in the collection are the first edition, Salisbury, 1766, the pirated edition which appeared in London in the same year, the first American edition which was published in 1772 and the first edition with the illustrations by Thomas Rowlandson, London, 1817. There are editions in French, German, Dutch, Swedish, one in phonetic spelling and one transcribed in Pitman shorthand. Some editions are well illustrated by such artists as Thomas Bewick, Thomas Rowlandson, John Thompson, Thomas Stothard, Richard Westall, George Dorrington, William Mulready, John Absolon, George Housman Thomas, Hugh Thomson, John Massey Wright, Henry Marriott Paget, Margaret Jameson, Edmund J. Sullivan, Arthur Rackham, Tony Johannot, Charles Emile Jacque, the New York physician Alexander Anderson, Charles Edmund Brock, and others. Memoirs concerning Goldsmith and his work appeared in many editions. Those by Samuel Johnson, George Moir Bussey, John Evans, Austin Dobson, George Saintsbury, John Forster, Sir Walter Scott, and the physician John Aikin, are worthy of special mention. One edition contains verses about Goldsmith by David Garrick and another edition consists of a dramatized version adapted for the theatre by Thomas John Dibdin.

1766

1. The vicar of Wakefield . . . Salisbury: printed by B. Collins, for F. Newbery . . . 1766. 2 vol.

First edition.

- The vicar of Wakefield . . . London: printed in the year 1766. 2 vol. Pirated edition.
- The vicar of Wakefield . . . 2. ed. London: printed for F. Newbery . . . 1766
 vol.
- The vicar of Wakefield . . . 3. ed. London: printed for F. Newbery . . . 1766.
 vol.
- The vicar of Wakefield . . . Dublin: printed for W. and W Smith, A Leathley, J. Hoey sen, P. Wilson, J. Exshaw, E. Watts, H. Saunders, J. Hoey, jun. J. Potts, and J. Williams. [1766]. 2 vol. in 1.

Date of publication appears in vol. 2 only.

6. The vicar of Wakefield . . . Dublin: printed for W. and W. Smith, A. Leathley, J. Hoey sen, P. Wilson, J. Exshaw, E Watts, H. Saunders, J. Hoey jun. J. Potts, and J. Williams 1766 2 vol. in 1.

1767

7. Le ministre de Wakefield . . . Londres. et se trouve à Paris: chez Pissot . . . Desaint . . . 1767. 2 vol. in 1.

Translation attributed to Charlotte Jeanne Béraud de Lahaie de Riou, marquise de Montesson.

8 The vicar of Wakefield . . . Dublin: printed for W. and W. Smith, A. Leathley, J. Hoey, sen. P. Wilson, J. Exshaw, E. Watts, H. Saunders, J. Hoey jun. J. Potts, and J. Williams 1767. 2 vol. in 1.

1770

 The vicar of Wakefield . . . 4. ed. London: printed for Carnan and Newbery . . . 1770. 2 vol.

1772

10. The vicar of Wakefield . . . Philadelphia: printed for William Mentz . . .1772. 2 vol. in 1.First American edition.

1773

The vicar of Wakefield . . . 5, ed.
 London: printed for T. Carnan and F.
 Newbery, jun. . . . 1773. 2 vol.

1776

The vicar of Wakefield . . . 2 ed. Berlin: sold by August Mylius . . . and printed at Altenburgh by Richter. 1776.

1777

 The vicar of Wakefield . . . London: printed for C. Ware, S. Bladdon, and T. Payne. 1777. 2 vol. in 1.

1779

 The vicar of Wakefield . . . 6. ed. Loncon: printed for T. Caman and F. Newbery jun. . . . 1779.

1780

- The vicar of Wakefield . . . Paris: printed by J. G A. Stoupe; and sold by J. N. Pissot, and Barrois, junior . . . 1780.
- The vicar of Wakefield . . . Newbury-port: printed and sold by John Mycall. [1780]. 2 vol. in 1.

- 17. The vicar of Wakefield . . . London: printed for Harrison & Co. . . . 1781.
- The vicar of Wakefield . . . London: printed for J. Davies; T. Smith; N. Taylor, and W. Thompson. 1781. 2 vol.
- Der Dorfprediger von Wakefield . . .
 Von neuem verdeutscht. 2. verbesserte Aufl. Hamburg und Altona, 1781.

1784

- 20. The vicar of Wakefield . . . 3. ed. Berlin: printed for August Mylius . . . 1784.
- 21. The vicar of Wakefield . . . Revised by Mr. D*** . . . 2. ed. Paris: sold by Theophilus Barrois, junior . . . 1784.

1787

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 Samuel Bladon and John Bew . . .
 1787.
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1789

24. The vicar of Wakefield . . . London: printed for Joseph Wenman . . . 1789.

1790

 The vicar of Wakefield . . . Glasgow: printed by J. and M. Robertson. 1790.
 vol. in 1.

1791

26. The vicar of Wakefield . . . Perth: R. Morison; Edinburgh: N. Chyne, 1791.2 vol.

1792

- 27. The vicar of Wakefield . . . London: printed for A. Law, W. Millar, and R. Cater. 1792. 2 vol. in 1.
- 28. The vicar of Wakefield . . . London:

- printed by Sammells and Ritchie, for E. Harding . . . and J. Good . . . 1792. Illustrated by Thomas Stothard.
- 29. The vicar of Wakefield . . . London: printed for Ogilvy and Speare, 1792.
 [Col.: Printed by T. Bensley . . .]
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1796

- 33. The vicar of Wakefield . . . Vienna: printed for R. Sammer . . . 1796.
- 34. Le curé de Wakefield. Traduit de l'anglais, par M. J. B. Biset . . . Londres: chez l'auteur . . . T. Cadell . . . & G. Davies . . . Deboffe . . . & Tindal . . . 1796.
- Der Dorfprediger von Wakefield . . .
 Von neuem verdeutscht. 3. Aufl. Leipzig: in der Weidmannischen Buchhandlung. 1796.

1797

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- 37. Le vicaire de Wakefield . . . Traduction nouvelle, par le [Pierre Louis] C[laude]. Gin . . . Paris: de l'imprimerie de Gay et Gide. 1797. 2 vol. Title and text in French and English.

1798

38. The vicar of Wakefield . . . embellished with wood cuts, by T. Bewick. Hereford: D. Walker, 1798. 2 vol. in 1.

39. The vicar of Wakefield . . . Stereotype edition. Paris: printed by P. Didot, the elder . . . Seventh year of the French republic [1799].

Notes signed "S.B.": pp. [196]-199.

1800

- 40. The vicar of Wakefield . . . [With a life of the author, and with verses about him by David Garrick.] Paris: printed for Ant. Aug. Renouard. 1800. 2 copies.
- 41. The vicar of Wakefield . . . Hannover: printed for Hahn, [?ca. 1800].
- 42. The vicar of Wakefield . . . To which is prefixed memoirs of the author [by Samuel Johnson] . . . Dublin: printed by T. Henshall . . . [?ca. 1800]. 2 vol. in I.

1801

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Illustrated with 6 plates by Thomas Stothard.

- 44. The vicar of Wakefield . . . In Gold-smith's: Miscellaneous works . . . A new ed. London, 1801, vol. 1.
- 45. The vicar of Wakefield . . . Salem: printed by Joshua Cushing, for Cushing & Appleton, 1801. 2 vol. in 1.

1802

46. The vicar of Wakefield . . . Manchester: Clarke & Co.; Liverpool: Jones; and Hull: Rawson & Rodford, 1802. 2 vol. in 1.

1803

Le ministre de Wakefield . . . Traduction nouvelle, par E*** A*** [Etienne Aignan] . . . Paris: chez F. Louis, 1803.

1806

48. The vicar of Wakefield . . . London: published by Vernor, Hood, & Sharpe . . . Lackington, Allen & Co. . . . Printed and sold by J. Robertson . . . Edinburgh, 1806.

1807

- 49. The vicar of Wakefield . . . Hanover: sold by the brethern [sic] Hahn, 1807.
- 50. The vicar of Wakefield . . . New-York: printed and sold by James Oram . . . 1807.

Illustrated by Alexander Anderson.

1809

- The vicar of Wakefield . . . Wellington: F. Houlston and Son, 1809. 2 vol. in I.
- 52. The vicar of Wakefield . . . To which are prefixed memoirs of Oliver Goldsmith by John Aikin. Walpole, N.H.: published by Thomas & Thomas, Cheever Felch, printer, 1809.

1812

- The vicar of Wakefield . . . Gainsborough: Stereotyped for Henry Mozley, 1812.
- 54. The vicar of Wakefield . . . new ed. London: printed . . . by Allen & Co. . . . 1812.

Illustrated with 6 plates by Thomas Stothard.

55. The vicar of Wakefield . . . To which is prefixed an account of the author's life . . . by . . . J. Evans . . . London: Albion Press: printed for J. & J. Cundee . . . [1812].

Woodcuts in text possibly by Thomas Bewick; engraving probably by William Marshall Craig and Luke Clennel.

1815

56. The vicar of Wakefield . . . London: printed for Whittingham and Arliss . . . 1815.

Illustrations by John Thompson.

57. Le curé de Wakefield, roman traduit de l'anglois . . . par M. de Russy . . . New-York: Joseph Desnoues, 1816. 2 vol.

Title and text in French and English. Published with poems by the author and the covering title: Chefs d'oeuvre . . . New York, 1815-1816.

1817

- 58. The vicar of Wakefield . . . London: published by R. Ackermann . . . 1817. Illustrated with 24 colored plates by Thomas Rowlandson.
- 59. The vicar of Wakefield: a melo-dramatic burletta, in three acts; first performed ... August 25, 1817. [Adapted] by Thomas Dibdin ... London: printed for John Miller . . . by B. McMillan . . . 1817.

1818

60. The vicar of Wakefield . . . London: printed for John Sharpe . . . by C. Whittingham . . . 1818-[1819].

Illustrations by Richard Westall and engraved title-page dated 1819.

1820

61. The vicar of Wakefield . . . With the life of the author, by Dr. [Samuel] Johnson . . . A new ed. carefully revised and corrected. London: printed for Dean and Munday . . . 1820.

(Cooke's pocket edition of select novels.)

1821

 Le ministre de Wakefield . . . nouv. éd., revue et corrigé. Paris: chez Roret et Roussel, 1821. 2 vol.

1822

The vicar of Wakefield. Chiswick: C. Whittingham, 1822.

Illustrated by John Thompson.

1825

64. The vicar of Wakefield . . . London: printed for Thomas Tegg . . . R. M. Tims, Dublin; and R. Griffin and Co., Glasgow. 1825.

Illustrated by John Thompson.

- 65. The vicar of Wakefield . . . London: published by Jones & Company . . . 1825. (University edition.)
- 66. The vicar of Wakefield . . . Paris: Baudry, 1825.
- 67. Le ministre de Wakefield. Traduction nouvelle, précédée d'un essai sur la vie et les écrits d'Olivier Goldsmith, par M. [Joseph François Gabriel] Hennequin. Paris: Brédif, 1825.

1826

68. Le ministre de Wakefield. Paris: chez Dauthereau, 1826. 2 vol.

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 De leeraar van Wakefield . . . Dordrecht: J. de Vos en compie. 1827.

1828

- 70. Der Landprediger von Wakefield . . . Aus dem Englischen Uebertragen von C. v. S. Quedlinburg und Leipzig: Gottfr. Baffe, 1828. 2 vol.
- The vicar of Wakefield . . . London: printed for John Sharpe . . . 1828-[1829].

Illustrated by Richard Westall. Engraved title-page dated 1829.

1831

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1833

73. The vicar of Wakefield . . . Paris: Baudry's European Library, 1833,

74. Le vicaire de Wakefield . . . Traduit par Charles Nodier, précédé d'une notice par le même sur la vie et les ouvrages de Goldsmith . . . Paris: Bourgueleret, 1838.

Illustrated with 10 plates by Tony Johannot.

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75. Le vicaire de Wakefield. Traduction nouvelle, par Louise Belloc; précédée d'une notice par Sir Walter Scott. Paris: Charpentier, 1839.

1841

76. The vicar of Wakefield . . . Illustrated . . . by George Dorrington, with a prefatory memoir of the author, by G. Moir Bussey . . . London: Willoughby & Co. . . . 1841.

1842

The vicar of Wakefield . . . With an account of the author's life and writings, by J. Aikin. New York: D. Appleton & Co., 1842.

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78. The vicar of Wakefield... With thirtytwo illustrations, by William Mulready, R.A. London: John van Voorst...

Illustrations engraved by John Thompson. Contains an autograph letter signed, from William Mulready, 1821.

1844

 Le vicaire de Wakefield. Traduction nouvelle par Charles Nodier. Avec un notice par le même sur la vie et les oeuvres de Goldsmith.

Vignettes par Tony Johannot. Paris: J. Hetzel, 1844.

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The vicar of Wakefield . . . With an account of the author's life and writings, by J. Aikin. New York: D. Appleton & Co.; Philadelphia: George S. Appleton, 1846.

1818

81. The vicer ov Wacfeld, and select poemz
... Lundun: Fred Pitman ... 1848.
Edition with phonetic spelling and half-title: Goldsmith's select wures.

1850

82. Le vicaire de Wakefield. Traduction nouvelle précédée d'une notice sur la vie et les ouvrages de Goldsmith et suivie de notes par Charles Nodier. 10 vignettes dessinées par T. Johannot, gravées sur acier par Revel. Paris: Victor Lecou, Hetzel et cie, [?ca. 1850.]

1853

83. Le vicaire de Wakefield, traduction de Charles Nodier. Illustrée par Jaques.
4. ed. Paris: E. Blanchard, 1853. 2
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84. The vicar of Wakefield . . . With illustrations by John Absolon. London: Grant and Griffith, 1855.

 The vicar of Wakefield . . . Illustrated by George Thomas. London: Joseph Cundall, 1855.

1859

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88. The vicar of Wakefield . . . New York: Albert Cogswell, 1880.

1881

 The vicar of Wakefield . . . Philadelphia: Porter & Coates, [1881.] (Alta edition.)

1883

- The vicar of Wakefield . . . With a preface and notes by Austin Dobson.
 London: Kegan Paul, Trench & Co. 1883.
- idem. Another copy. Large paper edition, consisting of fifty copies, of which this is no. 32.

1885

- 92. The vicar of Wakefield . . . Being a facsimile reproduction of the first edition published in 1766. With . . . a bibliographical list of editions . . . London: Elliot Stock, 1885. 2 vol.
- 93. Le vicaire de Wakefield, traduction nouvelle et complète par B.-H. Gausseron. Paris: A. Quantin, [1885].

Illustrated by V. A. Poirson. No. II of an edition of 100 copies.

1886

94. The vicar of Wakefield . . . With prefatory memoir by George Saintsbury . . . London: J. C. Nimmo, 1886.

Illustrated by V. A. Poirson.

1888

95. Le vicaire de Wakefield, traduction, préface et notes par Charles Nodier. Eaux-fortes par Ad. Lalauze, nouv. éd. Paris: Lib. des bibliophiles, 1888. 2 vol.

Ordinary edition.

- 96. idem. Another copy, no. 3 sur papier du Japon.
- 97. idem. Another copy, no. 22, sur papier de Chine.

- idem. Another copy, no. 39, sur papier Whatman.
- idem. Another copy, no. 100, sur papier de Hollande.

1890

- 100. The vicar of Wakefield . . . With a preface by Austin Dobson and illustrations by Hugh Thomson. London and New York: Macmillan & Co., 1890.
- idem. Another copy. Large paper edition.

1893

102. The vicar of Wakefield . . . Illustrated with etchings by Ad. Lalauze. London: Gay and Bird, 1893. 2 vol. (Édition Jouaust.)

No. 12 of a limited edition of fifty copies for the English market.

1903

103. The vicar of Wakefield . . . Chiswick: Caradoc Press, 1903.

No. 102 of a limited edition of 374 copies.

104. The vicar of Wakefield . . . Including John Forster's essay on the story, and containing . . . illustrations in colour by John Massey Wright . . . London: A. & C. Black, 1903.

No. 12 of an edition of 250 copies.

1904

105. The vicar of Wakefield . . . With colored illustrations by C. E. Brock. New York: E. P. Dutton, [1904.] (Series of English idylls.)

1910

- 106. The vicar of Wakefield . . . With twenty-four illustrations in colour by Margaret Jameson. London: Chapman & Hall ltd. [1910.] (Burlington library.)
- 107. The vicar of Wakefield . . . Illustrated by H. M. Paget. London: Ernest Nister; New York: E. P. Dutton & Co. [:ca. 1910.]

108. The vicar of Wakefield . . . Illustrated by Edmund J. Sullivan. London: Constable & Co., 1914.

No. 177 of an edition of 500 copies.

1916

109. Illustrated edition of the vicar of Wakefield . . . Intermediate style of Pitman's shorthand, Isaac Pitman. London: Sir Isaac Pitman & Sons; Bath: Phonetic Institute; Melbourne: the Rialto; New York; Toronto: Commercial text-book Co. [1916.] (Centenary edition.)

Text in shorthand.

1926

110. The vicar of Wakefield . . . Illustrated

with twenty-four coloured designs by Thomas Rowlandson . . [London]: Chiswick Press for Constable & Co. and Houghton Mifflin Co., 1926.

1928

111. The vicar of Wakefield . . . Edited . . . hy Oswald Doughty. London: Scholartis Press, 1928. (The Scholartis eighteenth-century novels, no. 4.)

1929

112. The vicar of Wakefield . . . Illustrated by Arthur Rackham. London; Bombay; Sydney: G. G. Harrap & Co., [1929.]

No. 371 of the English issue of 575 copies.

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NOVEMBER, 1943

NUTRITION UNDER WARTIME CONDITIONS

Harvey Lecture, May 20, 1943

V. P. SYDENSTRICKER

Professor of Medicine, University of Georgia School of Medicine

peace the nutritional status of their populations was determined by family income, prevailing customs in commercial distribution of essential foods, local agricultural trends and regional food habits. The advent of "total war" has forced the problem of providing adequate nutrition for every member of the commonwealth upon previously complacent governments. The only possible way to provide for an equitable distribution of food is by rationing. Our own experience with the ration is as yet too short for effects to be apparent but since our scheme of rationing seems to follow that of England, it may interest you to hear how the British have fared under their system.

There are many things which make our problems quite different from theirs, particularly the matters of production, transportation and distribution. In England distribution is a minor problem on account of the small size of the country. Transportation of supplies from the Western allies is a crucial matter and home production of many essential foods in adequate quantities is impossible. With us production is assured

if manpower is available, transportation and distribution are major prob-

If manpower is available, transportation and distribution are major problems on account of the great size of our country.

The whole background of wartime nutrition in England is reflected in the life of the people. Normal living has been interrupted to an extent greater than you may imagine. The blackout may seem a minor nuisance but during winter months, when it lasts from half past five in the afternoon until almost nine o'clock in the morning, it becomes more than a nuisance; it is depressing and it interferes, sometimes seriously, with the daily travel necessary for millions of workers. Bombing has destroyed or damaged one of every five houses in England. The bulk of the damage has been in the cities and large towns but there are few small towns without scars. Though very many damaged houses are still occupied, there are millions of people who have been made homeless and who are living with strangers, often in houses or flats already comfortably crowded. Even now evacuees from heavily bombed areas comfortably crowded. Even now evacuees from neavily bombed areas crowd many rural villages. Heavy bombings may not recur, but no day passes without hit-and-run raids by a few fighter-bombers; so airraid precautions have to be maintained everywhere. All civilians have their civil defense duties which are no longer voluntary. Fire-watching is required of practically all adults. All able-bodied men between the ages of sixteen and sixty-five who are not in the services are in the Home Guard. Heavy and light rescue squads are made up of men under and over military age who are accustomed to heavy labor. Repair and demolition squads are composed of men from the various trades whose technical knowledge fits them for such service. Emergency feeding and transport are largely in the hands of volunteer organizations of women. It may be said that everyone in England has two jobs, a regular one and a civil defense activity. When "incidents" do occur Civilian Defense may take up all the hours ordinarily spent in sleep, but that does not excuse anyone from the "regular job" the next day or night for it is the "regular job" which will win the war. This does not mean that the British are regimented. I believe that they resent restrictions of personal liberty much more than we do, but they have learned to cooperate in all things. This brings me to rationing, for nothing requires more complete coöperation than successful rationing and successful rationing means adequate if not optimal nutrition for all.

The wartime food program of Britain begins where all food programs should, in the ground. During peace approximately sixty per cent of England's food was imported. In addition, much of the phosphatic and potassic fertilizers used came from overseas. By various means the area of land under cultivation has been increased by about fifty per cent and home production of fertilizers greatly augmented. Crop loss from sodden land, plant diseases and insect pests has been reduced by extensive drainage projects and the application of measures to control bacterial and virus diseases of plants and to limit the propagation of destructive insects. The results of this effort have been impressive. The production of potatoes has increased by eighty per cent, of cereals by fifty per cent and there has been a great increase in the vegetable crops. On a tonnage basis the British have increased home production of food to about sixty-five per cent of total consumption. This increase, however, has been largely confined to carbohydrate foods and green vegetables. Sources of protein and fat, with the exception of milk have not and cannot be increased. It was recognized from the beginning that human food was of paramount importance and that domestic animals must not be fed food fit for human consumption. Pigs and chickens are direct competitors for food which people can eat; so their numbers were rather drastically reduced. Dairy cattle, on the other hand, are most efficient converters of food unfit for human consumption into milk; so every effort has been made to increase the number of milch cows. Pigs and chickens are still kept but mostly in small herds and flocks which can be fed on scraps and garbage. In addition to the great increase in land under the plough, every family is urged to cultivate an "allotment," the prototype of our victory gardens. There are millions of these allotments yielding potatoes and all sorts of vegetables which contribute significantly to the national food supply. With all this increase in home production Britain is dependent upon imports for most of the wheat and a tremendous proportion of the meat and fat upon which it must subsist.

The whole problem of rationing in England is much simplified by the facts that the Ministry of Food has control of supplies of foods at their sources and over most of the channels of distribution. The Ministry purchases all rationed foods and some important ones which are not rationed from the producers. In addition, there is control of the distribution and price of practically all important unrationed foods. Distribution is largely effected through regular trade channels and most of the administrative problems of distribution are handled by represen-

tatives of the various food industries. Even when the government requisitions stocks of certain foods, they are not taken away from the dealers but the Ministry assumes control over the disposition of the stocks. Control begins with the licensing of the original buyers of all food products and the prohibition of sale to any but a licensed buyer; these licensed buyers are almost always agencies representing or appointed by the Ministry of Food. The prices paid for a number of important foods are subsidized by the Government in order to stabilize the retail prices.

In the case of wheat, all purchase, importation and disposal is under the control of the Ministry of Food, though the actual business is accomplished by the Federation of Corn Trade Associations under a subsidy. The milling industry also is controlled by the Ministry of Food and since March 1942 no flour other than the National Wheatmeal of 85 per cent extraction has been produced. The baking of bread and biscuits and the manufacture of various breakfast cereals is controlled by licensing. Only four types of loaves can be produced by bakers and wrapping and slicing of bread has been stopped.

Oats, barley, rye, rice and dried pulses are under control orders similar to those for wheat. The use of cereals for brewing and distilling is regulated, as well as licensed. The bran from milled cereals is rationed for stock feeding as are supplies of unmillable grains.

The control of meat is very complete. The bulk of the supply originates outside England and is bought and imported by the Ministry of Food. Domestic food stock must be registered with the Ministry of Agriculture, when ready for sale the owner must notify the Ministry of Food. The cattle, hogs or sheep are then brought to central markets for grading and sale and are butchered at Government-controlled abattoirs. The auctioneers who conduct the sales and the owners of abattoirs are paid by the Ministry. Domestic bacon is cured by registered firms under license from the Ministry of Food. The exception to complete control of meat production is that the owner of hogs can secure a license to slaughter two animals a year for use in his own household. It is specified that the animals must have been owned for more than two months. The country is divided into eight Wholesale Meat Supply Areas in each of which the wholesale dealers are associated in Meat Supply Associations which, in turn, supply the retail dealers in their respective areas. Poultry, rabbits and fish are not rationed, but all

wholesalers are compelled to be licensed and retail prices are controlled. The distribution of fish is controlled by zoning in order to save transport.

Milk has been a special problem. The policy of the Ministry of Food has been to encourage consumption and to attempt to increase home supplies of fluid milk and imports of condensed and dried milk to meet the increased demand. Milk was controlled before the war by the Milk Marketing Board; this body has been maintained as the administrative and distributing agent though prices are fixed by the Ministry of Food and all imported condensed and dried milk is bought and imported by the Ministry. The direct consumption of milk has actually increased by about 20 per cent during the war though production has not been greatly augmented. This has been accomplished by prohibiting the use of fluid milk in baking, ice-cream manufacture and other food industries where dried skim-milk could be used. Dried skim-milk is also made available for household cookery. Both production and distribution of fluid milk are heavily subsidized and very little is allowed to be used for any manufacturing purposes. The resulting great curtailment in home production of cheese and condensed and dried milk has made these products items of great importance in the Lend-Lease program and in the scheme of imports from the Empire.

In recent times Britain has always been dependent on imports for adequate supplies of butter and other edible fats, and margarine has had a much greater place in the average diet than in this country. Because fortified margarine is a fair substitute for butter, no great effort has been made to increase imports of butter during the war. It is much more economical to increase imports of vegetable and marine oils from which margarine can be made. At the beginning of the war all edible fats were brought under the control of the Ministry of Food and the manufacture of margarine put under license. All margarine is fortified so that it contains approximately 5,000 units of vitamin A and 400 of vitamin D per pound.

Control of eggs proved more difficult perhaps than that of any other essential food. After several unsuccessful schemes had been tried the present arrangement was put into effect with apparently satisfactory results. All keepers of poultry owning more than 50 hens are required to sell all eggs more than those to which they are entitled by the ration to licensed buyers or packing stations. The price paid is more than the

retail ceiling price so there is little incentive for "black marketing." The loss is covered by Government subsidy.

Potatoes, onions, carrots and tomatoes are directly controlled by the Ministry of Food. Potatoes are the most important food crop in Britain, the great source of cheap calories and, at the present time, even more essential to the diet than bread. The Ministry guarantees the grower's price for potatoes and buys up surpluses. Distribution is effectively controlled and executed. Carrots and onions are bought from producers by the Ministry and distributed in a manner similar to that employed for potatoes. Tomatoes are one of the few good sources of ascorbic acid produced at home and every effort has been made to increase production. Practically all tomatoes are hot-house grown and owners of hot-houses are required to devote them to the culture of tomatoes for at least six months of the year. Tomatoes may be sold only to licensed or specified buyers.

Of fruits, only plums and apples are controlled; plums can be sold only to licensed buyers and apples only to specified classes of purchasers. The sale of berries and other soft fruits is not regulated, but prices are so fixed that it is profitable for growers to sell their crops to the jam manufacturers rather than to the public. Jam is an important rationed food and great effort is made to keep home production of it up to the requirements of the ration. To save small crops of soft fruits in rural areas many local preserving centers have been set up, sugar is supplied and the jam making done by voluntary workers. All the jam is taken over by the Ministry of Food. Oranges are imported in small quantities and are reserved for children.

All fresh vegetables which are in sufficient supply to make them of significance in the diet have price ceilings and during the season when they are available there is supervision, even direction of distribution. Efforts are made to foresee local surpluses and to provide for their distribution. Allotment gardeners are urged not to produce more than can be used in their homes; but when allotment surpluses do occur, there are arrangements for their diversion into established channels of distribution. Small surpluses of this kind may be sold directly by allotment holders to less fortunate neighbors.

All imported canned meats and canned or dried vegetables and fruits are bought and imported by the Ministry of Food for distribution under points rationing. The bulk of domestic canned and dried foods

also are reserved for distribution on points.

Sugar production has been greatly increased during the war so that the domestic supply almost meets requirements. The situation has been greatly improved by drastic restriction of the use of sugar in manufacturing and by the rationing of sweets as well as of sugar. The manufacture of chocolate and cocoa is licensed and restricted, and sweet chocolate is included in the candy ration.

Allocations of supplies of foods to wholesalers vary with the types of foods handled. Rationed foods and foods for which consumers must register with a dealer are supplied in accordance with the dealer's registrations. Unrationed foods are distributed on the "datum period" principle by which a dealer is supplied with a certain proportion of the food which he disposed of during a chosen period prior to the establishment of restrictions. Retailers in turn are supplied by wholesalers on the same principle. When there are significant shifts in population from one locality to another, both wholesalers and retailers are advised so that supplies can be diverted to meet demand.

Consumers' registration has been mentioned: this procedure further simplifies the problem of rationing. Each holder of a ration book is required to register with a retail dealer for all rationed foods except tea. It is required that one register with the same dealer for butter and margarine and for sugar and jam, no one is permitted to register with more than one dealer for any one article of food. This scheme enables the dealers to stock supplies in the most economical manner and at the same time assures the consumer of securing his ration when it is needed. It also increases the difficulties put in the way of "black marketing" since retailers can secure no more rationed foods than their customers' registrations entitle them to requisition from the wholesalers with whom they, in turn, are registered.

The actual ration has a considerable degree of flexibility. Meat is rationed by price rather than by weight; adults are entitled to one shilling and twopence worth of meat a week, children to half this amount. The average price of meat makes this worth approximately a pound a week for adults. If ground lean meat such as we call "hamburger," but the British call "mince," is bought, the amount is somewhat over a pound and there is no loss from bone. If cuts with bone are selected the buyer voluntarily takes the loss in edible return for his ration coupon. Most of the other rationed foods are dispensed by weight. Four

ounces of bacon or ham, eight ounces of edible fat, usually distributed as two ounces of butter, four of margarine and two of cooking fat, eight ounces of sugar and two ounces of tea are the weekly allowance. The cheese ration varies with supplies available, from four to eight ounces a week. Syrup, jam, honey and marmalade are rationed by the month, one pound per person. Usually there is choice between the available sweet spreads. At Christmas mincemeat is available on the jam ration coupons and suet for plum puddings on the fat coupons. Milk and eggs are rationed on a priority scheme which will be mentioned later. All canned fish and meats, vegetables, fruit and some canned soups as well as rice, dry breakfast cereals, tapioca, biscuits, dried fruits and pulses are rationed on "points." No registration is required for "points foods" and the demand for them is adjusted to supplies by frequent changes in the "points" value of different items. Foods in short supply have a high points value, slowly moving articles are often sold by lowering their points value, and it is possible to slow up consumption of popular foods by raising their points price. The number of points coupons issued for different ration periods may vary with the supplies in hand. At the start of points rationing only 16 coupons a month were issued to each ration-book holder, late in 1942, 24 coupons a month were available.

The British scheme of rationing, like ours, is aimed at providing everyone with an equal amount of food. There are certain provisions made for altering the ration for specific groups of the population. Children get only half the amount of meat allowed adults but are given priority for milk and eggs. Diabetics are allowed extra amounts of meat and edible fats for which they surrender their sugar coupons. Persons with hypoglycemia can get extra sugar; those with nephrosis, extra meat. Patients with sprue and steatorrhea are allowed additional meat for which they give up their edible fat coupons. Sufferers from peptic ulcer, dysentery and various conditions interfering with swallowing or mastication have priority for milk and eggs, and provisions are made for the various dietary requirements of patients in hospitals and sanitoria. Vegetarians are permitted extra cheese rations, but must surrender their meat and bacon coupons. Workers in various trades and occupations who have no access to hot meals in the middle of the day are given 12 ounces of cheese a week in addition to the regular ration. Miners, forestry and agricultural workers, Land Army girls, railway and canal workers and charcoal burners are some of the groups receiving the extra cheese ration. During the harvest season farmers are allowed special amounts of tea, sugar and margarine to enable "tea" to be served to the workers in the field, and owners of buildings and businesses can secure extra tea for fire-watchers on duty on their premises.

An interesting and significant part of the rationing program is the milk policy. It is the purpose of the Government to increase the consumption of milk as much as possible by those who need it most. To this end, milk is distributed by priority. Normal adults can obtain two pints a week if supplies are abundant; if supplies are short, they may get part or none of this, all available milk then going to priority consumers. The priority groups are children, expectant and nursing women, invalids and certain classes of workers. Infants under a year old get seven quarts of milk a week, children between one and six years old and pregnant and nursing mothers get seven pints, and children six to eighteen years old get seven half pints a week. Invalids may have what the doctor orders up to seven quarts a week. Workers in certain munitions and chemical factories are provided with one-half pint of milk a day. Milk for children under five and for nursing and pregnant women is sold at the nominal cost of 2d (4 cents) a pint and if the family income is below 40 shillings a week, can be obtained free.

In addition to this "free and cheap milk scheme" which is part of the war rationing, the school milk program, which was in force before the war, is being continued. This furnishes each school child applying for it, 1/3 of a pint of milk a day at a cost of 1s. 2d. (24 cents) a month; children unable to pay this nominal price receive the milk free. At the request of the school physician any child is furnished an extra 1/3 pint free. The entire cost of this program is borne by the Government.

The requirements for fluid milk for women and children are such that little is available for cooking purposes; these are provided for by making skimmed milk powder available on a non-priority basis.

Eggs, like milk, are distributed by priority. At best eggs are in very short supply, the ordinary consumer is allowed two eggs a month. Children under six and nursing and pregnant women, together with invalids suffering from specified diseases, get four eggs for each one allocated to the ordinary consumer. In practice shell eggs simply are not available for normal adults, the entire supply being required for the priority groups. During the last year supplies of dehydrated eggs from this

country and Canada have made it possible for ordinary consumers to

secure a tin of egg powder per ration period in lieu of fresh eggs.

Priority distribution also is applied to the distribution of oranges and other rich sources of ascorbic acid as well as to codliver oil. Oranges are reserved for children under six; and when shipments are not sufficient for distribution over the whole country, a rota system of supply is applied, oranges as they become available being sent to different sections of the country in rotation. In theory oranges on sale are for children under six only for the first five days of the week, if any are left on Saturday they may be purchased for adults. In practice the supply never lasts for five days so that adults, unless they steal from children, which they never do, do not taste oranges. Black current juice and puree are reserved for infants under two and since December 1941, these products have been distributed free. Rose hip syrup, another excellent source of ascorbic acid, is also available for infants, and in 1942 concentrated orange juice prepared in this country was added to the "free or cheap" sources of vitamin C for infants. All children under two receive codliver oil free. Codliver oil and one of the vitamin C preparations are available everywhere through local Maternal and Child Welfare centers and the Local Food Offices.

Unrationed foods are most important in the British food scheme. As has already been mentioned, fish, shellfish, poultry, rabbits and game are off the ration. All "offals" and the 45 per cent meat "war sausage" also are unrationed, as are bread, potatoes and all vegetables and fruits. Fish are not abundant because of the requisition of most of the fishing fleet by the Admiralty. Available poultry is made up of cockerels and superannuated hens. Rabbits are abundant, in fact, they are a serious pest to farmers and furnish a significant contribution to the meat supply. Game is scarce and distinctly a luxury. Variety in vegetables is small; cabbage, Brussels sprouts, peas, string beans and broad beans, spinach, beets, turnips, carrots, tomatoes and leeks are the usual ones available and of these, cabbage, sprouts and carrots are the only ones produced in adequate quantities. Still it is the unrationed foods that enable Britain to carry on.

Another important phase of the British food policy is the development of communal feeding. The Ministry of Food has promoted communal feeding because it saves fuel and waste of food and also saves much time for workers of all types. In addition, it improves the nutrition of the entire family of each person eating at a communal feeding place since all meals served in "British Restaurants," works canteens and school canteens are "off the ration" and increase the amounts of food available for the family at home. What is still more important from the standpoint of the war effort it enables hundreds of thousands of women to be engaged in war industry by freeing them from the necessity of preparing a noon meal.

The establishment of "British Restaurants" is at the discretion of local authorities, but the Ministry of Food finances the conversion of premises, covers losses in operating expenses and furnishes expert culinary and dietetic advice. The Ministry also maintains a central pool of cooking and dining equipment for distribution to feeding centers and aids in securing priorities for materials of all sorts.

Factories employing more than 250 persons are required to maintain canteens to furnish a hot meal at noon and, if necessary, at midnight. Smaller factories often club together to provide a common feeding place. The Ministry of Labor determines where work canteens are needed and the Ministry of Food coöperates in establishing them. Not infrequently where there are a number of small factories some distance apart a communal kitchen is established where food for all is cooked and distributed in insulated containers to the factory messes.

School feeding of sorts was common in England before the war but has been greatly expanded by the combined efforts of the Board of Education and the Ministry of Food. It serves the double purpose of increasing the food intake of the children and of freeing their mothers to perform essential work in industry. A majority of the larger schools have their own kitchens and the preparation of the school meal is part of the training of the older girls in Home Economics. Small schools usually secure food already cooked from the communal kitchen which, in many instances, is a nearby British Restaurant. School meals are subsidized up to 95 per cent of their cost by the Board of Education.

The food served in these various communal feeding places is much alike; dinner consists of soup, a full ration of meat or a liberal portion of fish, potatoes, one vegetable, often a salad, a dessert, bread, margarine and tea. Meals usually are as good as are found in the cheaper restaurants. British Restaurants and works canteens charge from 10d. (18 cents) to 15. 2d. (24 cents) per meal. School canteens charge from 4d. to 6d. and provision is made for free meals for "necessitous" children.

It is difficult to estimate the contribution to the wartime efficiency of England that is made by the community feeding centers. Millions of meals are served "off the ration" daily, conserving equal amounts of rationed foods for home consumption. The morale effect is great; untold millions of man-hours and woman-hours have been saved for vital war industries. School children are assured of a hot nourishing midday meal that makes no demands on the family rations or on the time of a mother who may be engaged in important war industry.

The only serious objection to communal feeding is that the food is cooked in such quantity that it is very difficult to use methods that are conservative of the heat labile vitamins. Green vegetables and potatoes are cooked in steam kettles, then held in hot-boxes, sometimes for hours before being eaten. When food is cooked in communal kitchens and distributed in insulated containers, the situation is even worse. It is likely that at least 50 per cent of the ascorbic acid in all foods is destroyed in the cooking, and when hot storage is employed the loss may reach 100 per cent.

So far I have discussed the British rationing scheme and the devices employed to better the general nutritional status of the nation during wartime. You may be interested to hear how people actually fare under the British ration.

At home the chief difficulty is the meat ration. If the family ration is conserved, a "joint" can be bought on Saturday if the dealer has one and roast meat can be served for dinner, hot on Sunday, cold on Monday and as hash on Tuesday; after that rabbit, fish, offals, poultry and "points" must be depended upon for the rest of the week for the main meal. For breakfast, oatmeal, bacon or "sausages," bread and jam and tea are the rule. For lunch, soup made from vegetables, a very small portion of meat, either cold from the Sunday joint or mince, potatoes, cabbage, sprouts, carrots or turnips, pudding and tea. For dinner, more soup, perhaps leftover meat from lunch, lacking that, perhaps fish or rabbit or a scramble of eggs made from egg powder, potatoes, perhaps a vegetable as at lunch, pudding again and bread and butter and tea. Cheese is often substituted for meat either at lunch or dinner.

At ordinary restaurants the menu is much the same, often even more restricted. Breakfast is a difficult meal for a restaurant liver in England because variety is almost impossible. Restaurant lunches almost uniformly consist of soup, mince in some form, cabbage or sprouts,

potatoes and some dessert, usually a pudding. Dinners are not materially different from lunches except that cheese is frequently provided for dessert. Rarely points meats are available in restaurants.

In luxury restaurants where heavy cover charges are made the cooking is apt to be better and much use is made of "off the ration" items so that really excellent meals can be obtained if one is willing to pay the price. There many types of sea food and vegetables neither rationed nor controlled may be had and such things as gulls' eggs, out-of-season asparagus and mushrooms, winter tomatoes and real salads can be found.

Restaurant meals are rather rigidly controlled though they are all off the ration. Five shillings is the maximum price which can be charged for food at any meal, and in any one meal no more than one "main dish" and one "subsidiary dish" or two "subsidiary dishes" may be served. A "main dish" is one containing meat, poultry or game (excluding soups containing not more than 5 per cent by weight of these foods) or containing more than 33-1/3 per cent by weight of fish or eggs (excluding scrambled eggs or omelettes made from dehydrated eggs). A subsidiary dish is one containing less than 1/3 by weight of fish or eggs, cheese counts as a subsidiary dish when taken for dessert. Hotel meals are subject to restaurant regulations and no one is allowed to remain in a hotel for more than five days without turning his ration book over to the management. Restaurants procure food under license and receive allotments based on the average number of meals served in a datum period.

Luxury restaurants are permitted to levy cover charges which may run to twice or even three times the five shillings maximum charge for food. In theory these cover charges are to provide music and other entertainment, in fact they pay for the unrationed variety foods which are procurable. This practice is winked at by the authorities on account of the high morale value of these bright spots in the blackout and also because the foods which they feature are in such short supply that no general distribution of them would be possible. All such establishments are under constant surveillance for black market practices, and if found to be violating the law they are subjected to extraordinarily severe, usually confiscatory penalties which combine loss of license, imprisonment of the proprietor and a huge fine.

It is true that the rich man in England can still buy more to cat than the poor man, but what he can buy is more variety than nutritional

value. The ration has, in truth, leveled out the diet for all practical purposes. The rich certainly eat less and the poor eat more of the foods which are essential to good nutrition. For an overwhelming majority of the people the diet under rationing is incredibly monotonous. The British cannot raise a great variety of vegetables and fruits on account of climatic conditions. Imports have been reduced to a minimum to release shipping for the transport of our men and the munitions necessary for them to wage a successful war. Many national dishes are impossible to prepare under wartime conditions. Roasts and steaks are out of the question under rationing. Fish and chips are a luxury on account of the scarcity of fish and cooking fat. Clotted cream is illegal and the fine English cheeses are only a happy memory because the demand for fluid milk has almost eliminated the production of cheese. Wiltshire bacon and hams are not found in the market because largescale hog raising is not possible and all cured pork is on the ration. Oatmeal, a little bacon or "sausage," a little jam or marmalade, bread, margarine, occasionally some egg powder as scramble or omelette, a little meat, usually "mince," fish or rabbit occasionally, potatoes, cabbages, Brussels sprouts, carrots, boiled puddings and cheese, these are what the average Briton lives upon. In summer there are a few green vegetables, peas, broad beans, string beans, with now and then a treat of fresh fruit or salad. The British people do not like it any more than would you, but they carry on in a most exemplary fashion.

However monotonous the diet under rationing may be, the nutritional status of the British people has not yet been seriously depressed. It is the opinion of all Medical Officers of Health with whom I have talked that the general health has improved during the war. It seems to be true that there has been a definite loss in weight among the well-to-do class, but against this there is evidence of improvement in the nutrition of the working class. Poverty such as we know in our large cities and in our backward rural areas does not exist in England. Food habits there are, in the main, good. Bread and potatoes furnish the bulk of the calories in the diet; both the 85 per cent extraction bread and potatoes are good sources of the B group of vitamins and potatoes are an important source of ascorbic acid in the quantities in which they are eaten. In fact during the winter months potatoes and vegetables of the cabbage family are practically the sole sources of vitamin C for the entire population with the exception of children under six. Animal sources of pro-

tein and of vitamin A are not abundant. The amount of meat available furnishes approximately 18 to 20 grams of protein a day, the intake of vegetable protein is ample to bring the total protein of the diet up to requirements. Butter and margarine furnish relatively small amounts of vitamin A, the weekly ration does not contain one day's requirements but the amounts of carotene available from carrots, cabbage and sprouts are probably adequate. The far content of the ration is quite low; this probably accounts for the weight-loss among the higher income groups of the population. Iron and calcium are also at what are thought to be minimal levels for adequate nutrition and there is a strong feeling on the part of some of the British nutritionists that the amount of phytic acid present in the 85 per cent flour may interfere with the proper absorption of these elements. In short the British ration is ample in calories but low in animal protein and in fat. The average intake of vitamins is, with the exception of the B group, considerably below the levels regarded as desirable; it is doubtful whether the average adult secures more than 1500 units of vitamin A and 20 milligrams of ascorbic acid daily.

In spite of having subsisted on this ration for three and a half years. the people appear to be well fed and there are no definite clinical evidences of vitamin deficiency diseases. My own observations were entirely clinical and were confined to selected groups of the population chosen because there was reason to suspect that their nutrition was below the average. Nearly five thousand people were examined in various parts of England and Scotland, nearly half were older school children and adolescent workers. Three elderly people had typical Bitor's spots without other evidences of deficiency of vitamin A. Mild folliculosis was common among children and women but could not be related to deficiency of vitamin A. I saw one mild pellagrin and eight women who showed characteristic lesions of riboflavin deficiency. Approximately thirty-five other persons had corneal vascularization of the pattern that may be due to riboflavin deficiency but showed no other evidences of malnutrition. No scurvy was seen. Gingivitis is exceedingly prevalent in most parts of the country and is associated with severe dental caries in many instances. The relation of this gingivitis to low intake of ascorbic acid is not yet established. Medical officers of health, dentists and school medical officers with whom this matter was discussed were unanimous in the opinion that neither gingivitis nor caries are more prevalent than before the war. Therapeutic tests with ascorbic acid have so far been negative except for one test carried out in Dundee in one of the large hospitals; there the gingivitis of a number of patients was definitely improved by large doses of vitamin C. Many children in Scotland show evidence of old rickets but it seems unlikely that any of the findings I have mentioned are related to the present ration.

Where biochemical methods and physiologic tests have been employed in conjunction with clinical examination some suggestive results have been obtained. Dr. A. P. Meiklejohn found exceedingly low values for plasma ascorbic acid in subjects examined in South Wales in the early spring of 1942, as the season progressed and green vegetables and a small supply of cherries became available the values increased to reasonably satisfactory levels. No clinical condition suggesting scurvy was seen by him. In the same locality a small group of women with marked folliculosis had low blood levels of vitamin A, amounts of the order of 60 I.U. per 100 cc. of blood while the average for the community was 90 I.U.; no person in this group had any defect of dark adaptation or other evidence of deficiency of vitamin A. The same observer found that a small number of the women examined in Lancashire as well as in Wales had slight reduction of plasma protein values, but no edema was found which was attributed to hypoproteinemia. A number of observers in various sections of England and Scotland have reported an apparent increase in simple hypochromic anemia during the past year. The subjects examined have been older school children and young women. The grade of anemia observed has not been severe, hemoglobin values were of the order of 13.0 to 13.5 grams per 100 cc. of blood. Extensive surveys of hemoglobin and red cell values in many localities are now under way.

The general health of the British people has remained good. There have been no epidemics, in fact, the ordinary infectious diseases have been somewhar less prevalent than during the pre-war period. There has been a definite increase in the incidence of pulmonary tuberculosis among young women and of tuberculous meningitis among young children. This may in some way be related to nutrition but may also be explained by the crowding together of great numbers of girls in factories and hostels, and by the increased consumption by children of unpasteurized milk.

It may be said in conclusion that the Ministries of Agriculture and

of Food have rendered a tremendous service to the British people in providing a ration which has leveled out the food habits of the nation and provided enough of everything for everybody. There seems to be no question that the poorer section of the population has benefitted from rationing. Poor children are getting more milk than ever before and very many are getting more oranges and other sources of ascorbic acid. People everywhere have become interested in practical nutrition and have come to depend on the information furnished by the Ministry of Food regarding the best use to make of foods of all descriptions. It must be repeated that the diet is monotonous and that well-to-do people are not nearly so well fed as was their habit before the war, but the lessons learned from wartime rationing promise to make a lasting improvement in the nutrition of Britain in the days when sea lanes are open again and an orange can be had to replace those daily pounds of potatoes.

(No formal bibliography can be furnished. Free use has been made of information contained in various reports of the Ministry of Food and the Ministry of Health. Much factual information regarding the ration is from the brochure, "Food Control in Great Britain," The International Labor Office, Montreal, 1942.)

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December 1914, at the fourth centenary of Vesalius' birthday, anatomists and historians from all parts of the world were expected to gather in Brussels, where a solemn celebration of the anniversary had been prepared. But at that time the invader occupied Belgium, the University of Louvain, where he had studied, had been destroyed and the international homage to the founder of modern anatomy could not take place. Nor, for the same reason, is this possible this year, at the fourth centenary of the publication of the Fabrica. Free scientific activity is suspended or hampered all over continental Europe and international meetings are no longer possible. It seems to have been fate that, during Vesalius' life and even after his death unanimous recognition of his greatness always met with some obstacles. In this country, however, where the appreciation of his merits found eloquent expression in many studies of prominent scholars such as William Osler, Harvey Cushing, Edward Clark Streeter, Fielding Garrison, Henry Sigerist and othersin this Academy of Medicine under the auspices of which a magnificent reproduction of the Fabrica's engravings from the old blocks was published, the great historical event had to be remembered. I have taught for many years at the same University and in the same place where four hundred years ago students coming from everywhere listened to the words of Vesalius and I will try to outline his wonderful activity at the school with which his name is indissolubly connected.

On the morning of the fifth day of December, 1537, a solemn assembly was gathered in the sumptuous hall of the bishop's palace at Padua. The vicar of the Pope, the professors and members of the College of Doctors in their gorgeous gowns were present, and Francesco Frigimelica, prior of the College, after stressing in a flourishing, Latin dis-

^{*} Read January 13, 1943 before the Section of Historical and Cultural Medicine of The New York Academy of Medicine.

course the merits of Andreas Vesalius, of Brussels, who in previous examinations had furnished ample proof of his proficiency in medicine, conferred upon him the degree of Laureate Doctor of Medicine. The professors who placed their signatures on the elaborate document knew very well that the young man was already destined to an important place among them; the following day he was nominated "by the illustrious Senate of Venice, which is by far the most liberal in the endowment of the higher branches of learning, Professor of Surgical Anatomy," and he immediately began his teaching and dissecting. The fact that the official appointment came on the day after the graduation suggests that the Senate and the professors evidently had had ample opportunity of knowing the man whose academic career began in such an unusual way.

Padua, as the center of the scientific Renaissance, was at that time at the peak of its glory. While religious wars were raging all over Europe, hundreds of foreign students were grouped in the "nations," which offered hospitality to the newcomers and were organized with perfect discipline, as centers of friendship and of learning. To mention only one figure: in the second half of the 16th century, the German "nation," which comprised the Flemish students, had an enrollment of 977 members, who attended the medical school. In occasional fierce competitions with other universities, of which we possess many records, the Venetian Senate tried to engage the most famous teachers for the school, and according to the new trend of medical doctrines, anatomy was evidently designed to be the center of medical studies. Padua had played in this field a remarkable role. Alessandro Benedetti had taught anatomy at the end of the 15th century, with great success, and had published a work on anatomy, dedicated to the Emperor Maximilian I, stressing the need for anatomical dissections, giving an exact account of their performance, and a description of the anatomical theater. The fact that Benedetti insisted upon the need for a permanent theater, instead of the temporary ones which were then in use, proves that regular and frequent dissections were part of his program. In the first part of the 16th century, in the flowering of the Renaissance in art, an impetuous desire for knowledge and inquiry into all problems of Nature, was manifest, and anatomical studies were initiated everywhere in Italy. In Bologna, Antonio Benivieni, the greatest of pre-Vesalian anatomists, had published, in 1502, his book on anatomy, and Berengario da Carpi,

commenting on Mundinus, had begun to doubt the teachings of the classics. Alexander Achillini, called Magnus Alexander, Professor in Padua, later in Bologna, had published, in 1524, a book with many corrections of Galenic anatomy, with the first correct description of the cecum, the bile duct, and the suspensory ligament of the liver. In Padua, and later in Pavia, where he died as a young man, Marcantonio della Torre, anatomist and friend of Leonardo, had first stressed the necessity for drawing directly from nature as a help to both teachers and students. But these were isolated attempts, public dissections were rarely performed, and outside Italy, in Germany, in France and in the Low Countries, anatomy was taught only from books or from animals. Galen was still considered the authority and a mighty revival of his influence was at hand. Humanism had begun a strong fight against the Arabian authors, and the first move against them was in defense of Galen whose teachings the Arabs were accused of having plagiarized and distorted. The Neo-Galenic Academy of Florence had published, in 1533, a violent attack "against Avicenna and the neotheristic doctors who neglecting Galen accepted barbaric doctrines." Paris was the stronghold of Galenism, and solemnly proclaimed the infallibility of the prince of physicians.

Vesalius belonged to a family of doctors who had been connected with the Imperial court, the University of Louvain and the Galenic tradition. At the medical schools of Louvain and Paris, two ardent Galenists, Guenther of Andernach, a learned humanist, of whom Vesalius later said that he never had used a knife except at table, and Sylvius, the leader of the Paris faculty, taught anatomy. But the young Vesalius was animated by an unquenchable thirst for learning and researching, personally and independently. He soon recognized that the system of teaching anatomy was wrong. "The derestable procedure now in vogue is that one man has to carry out the dissection of the human body, while another gives a description of the parts. The lecturers are perched up aloft in a pulpit, like jackdaws, and with a notable air of disdain, they drone out information about facts they never approach at first hand, but which they merely commit to memory from the books of others, or of which they have descriptions before their eyes; the dissectors are so ignorant that they are unable to explain the dissections to the onlookers, and botch what ought to be exhibited in accordance with the instruction of the physician, who never applies his hand to the

dissection and steers the ship out of the manual, as the saying goes. Thus, everything is wrongly taught, days are wasted in absurd questions and in the confusion less is offered to the student than a butcher in his stall could teach the doctor."

In Paris, Vesalius had contested for a human skeleton with a pack of hungry dogs in a grave yard; at Louvain, he often waited near the gallows outside the town, trying to procure corpses or bones, and once climbed the gallows in order to take down a skeleton which he brought home in separate parts. The difficulties of dissecting and of teaching brought him to the decision to repair to Padua which he rightly believed to be the one place where his activity could develop freely. How he succeeded in acquiring the confidence of the Senate and of the Paduan professors, we do not know; but it is certain that in Venice, where anatomy was eagerly taught at the College of Physicians, he explained his program and obtained the promise to have the corpses he needed for his lectures.

In Padua the teaching of anatomy was generally committed to the professor of surgery and the dissections were usually done by the surgeons, despised by the learned doctors. Vesalius was appointed professor of surgery primo loco, in first place, on the condition that he had to lecture on anatomy and to perform the dissections. We know that actually he also taught surgery and lectured on tumors and on fractures. But anatomy was the chief object of his lectures; in official documents he is often praised as anatomist and teacher of anatomy with no notice of his lectures on surgery. In a document of 1541 he is nominated lector, dissector and ostensor in anatomy.

In December 1537, Vesalius began his dissections and we know from contemporary sources and from the reports to the Senate, that his success was beyond all expectation. More than 500 students and doctors, and many distinguished and learned men, crowded his classes. The dissections sometimes lasted three weeks, in morning and afternoon sessions. The professor took great care to have a sufficient number of corpses at his disposal, and when these could not be secured, he dissected animals and performed vivisections. He began his teaching by summarizing briefly Galen's description of the part he was going to show, and then he proceeded to the demonstration, dissecting and accurately preparing the part by himself, calling sometimes upon one or another of the students to assist him, with no further reference to the

text. Upon the request of the students, he prepared a delineation of the veins "which proved to be so pleasing to all the physicians and students that they strenuously urged me to supply a description of the arteries and the nerves." He went on drawing sketches for the students, and was so convinced of their usefulness, that, in 1538, he published the Anatomicae Tabulae, three of which were designed by himself, three by his countryman, John Stephen Calcar, a pupil of Titian's and a fine artist. The success was so great that immediately the Tables were reproduced and plagiarized in Marburg and Cologne, in Augsburg, Frankfort and Paris.

Everyone who compares these tables, born in the dissection room, with the "fugitive sheets" of anatomy, which were widely used at that time, and were derived from old, conventional patterns, is immediately aware of the great progress. These tables, which represent a remarkable achievement, show however, that Vesalius had not yet broken away from classic anatomy. The descriptions of the liver in four lobes, of the sternum in seven parts, of the uterus with horns, correspond not with reality, but with Galenic teaching. Vesalius still accepted the authority of the Ancients, and when in need of a textbook, he did not think to write one himself, but prepared a new edition of his teacher's, Guenther von Andernach's, Institutiones Anatomicae, correcting many errors of the original text, which he generously attributed to misprints. When the Venetian printers, Giunta, entrusted him with the editing of the anatomical books of Galen for the complete Latin translation in five volumes, for which no expense was spared, Vesalius eagerly accepted. His vast classical education enabled him to accomplish this difficult task. He had called Galen "the divine teacher, the author of all good things," and had considered galenism unassailable but now, during the assiduous study of Galen's works in the original text, an essential change in his judgment took place. It is once more the characteristic proceeding of the Renaissance, from Humanism and blind reverence of the classic masters, to independent criticism, and from criticism to rebellion against dogmatic authority. In the new edition Vesalius corrected some errors of Galen and Augustinus Gadaldinus, the anatomist, tells that "Vesalius improved Galen's books on anatomy to such an extent as to alter them in many places." The accurate study of the text, the comparison of different sources, and the contemporary control of Galen's assertions by means of his own observations, brought

him finally to the conviction that Galen's mistakes derived from the fact that he had never dissected a human corpse and had believed it to be right to accept the findings on animals as conclusive for human anatomy. Galen, said Vesalius, was "cheated by his monkeys, and in the manifold divergence of the human body from that of the monkeys, had hardly noticed anything except in the fingers and the bend of the knee." The whole study of anatomy had to begin anew.

Starting from this conviction, Vesalius continued his work as teacher calling the attention of his pupils to the differences between the classical texts and the evidence of personal observations and collected accurately the descriptions of his findings and his discoveries. His intense, continuous activity appears wonderful. Encouraged by the students and by many of his friends, among whom he named with deep gratitude J. B. Montanus, the famous professor of medicine, and M. A. Genova, professor of philosophy at Padua, he prepared the two great books, the De Humani Corporis Fabrica and the Epitome. The Epitome was according to his intentions "the guide, index, and compendium of the Fabrica." It was dedicated to the students as a handbook for dissections and at the same time to physicians and surgeons, who, preparing for an operation, had to recall the position and the form of a bone or of an organ. The Fabrica had to be, and in fact was, the first complete and systematic description of the human body as "a fabric, a wonderful structure, according to the work of the Supreme Creator and the Divine Artist, Nature." Anatomy had to be taught as the "history of the human body, with perfect truth and absolute exactness."

The Fabrica is therefore more than a classic book of anatomy: it is from the frontispiece to the last page, a declaration of principles, a program of studies and an autobiography, from which the personality of the author emerges fresh and living. The title-page gives us the picture of the anatomical theater, as Vesalius visualized it, the figure of the teacher in the attitude of a challenger who proclaims his beliefs, and is surrounded by an attentive and astonished audience. In the middle of the picture is the corpse, around which the whole scene centers. At the top of the theater, Vesalius' laurelled coat of arms stands as an affirmation of confidence in ultimate victory. In the portrait drawn by Calcar, on the third page of the book, Vesalius appears again examining the muscles of the right arm, in the act of resolving an anatomic problem, with which, we know, he was especially concerned. He does not wear

the traditional gown of the professor, but is clothed in the gorgeous brocade of the patrician. In front of him, on the table, is an open book, not the traditional text of Galen, but the manuscript of a chapter of his Fabrica.

The preface, addressed to the Emperor, to whom the book is dedicated, is, like all prefaces of that period and many of later times, redundant in rhetorical phrases. The author correctly foreseeing that his enemies would accuse him of heresy, declares that he respects the doctrine of the classics, and that he only wants anatomy restored to its ancient place of honor. The flatteries of the prince, the protestation of devotion belong to the arsenal of all writers who felt the necessity of finding a sure and mighty protector against the strict censorship of the ecclesiastic authorities, and they often were the label which was expected to cover the contraband.

Vesalius' book first brings to the teaching of anatomy the contribution of objective observation and exact intelligent criticism. Through the penetrating eyes and the agile hand of the young anatomist the Fabric of the human body is revealed and shown in its proper structure, so that we can really speak of numberless discoveries. He lifted the veil which had obscured the real shape of things and therefore he put in his work the foundation of a new system of studying, of teaching, of thinking. In the Fabrica the subject is systematically ordered in such a manner that the reader may have a complete and exact knowledge of the human body as a whole and of all its parts, finding for everyone the perfect description of its form and functions. Vesalius is at the same time the anatomist, the surgeon and the physician who conceives medicine as a whole and states that anatomy has to be "the firm foundation of medical art and of its essential doctrines." He states that surgery has to be equal in dignity to medicine, and that all who want to be physicians have to study it diligently. Dealing with Galen, Hippocrates and Celsus, with Aristoteles and Avicenna, whom he often refers to, he pronounces an independent and courageous judgment, showing the way for objective research. He claims the right to perform vivisection on animals, and considers the problems of respiration and circulation with a clear mind. He is above all a teacher, and as a teacher he appears in direct communication with his pupils, never posing as an authority, and constantly inciting them to examine, to experiment, and to judge for themselves.

The accord between the text and the figures is unprecedented. We know that anatomical illustrations at that time were considered by the Galenists as not only useless, but a hindrance to the understanding of anatomy, and the figures of the Fabrica aroused a bitter controversy, led by Sylvius and his school. But Vesalius had correctly understood the importance of the illustrations for his book, and his choice of artist was very fortunate. Stephen van Calcar's name is indissolubly bound to Vesalius' glory. His drawings gave to the book the incomparable worth of both a reliable guide through the paths of anatomy and of an admirable work of art. The large figures appear erect in plastic attitudes. Look at the figure of the skeleron standing in the position which was supposed to have given Shakespeare the inspiration of Hamlet's monologue, regarding pensively the skull which rests on a marble base, which is inscribed: "Man lives through his genius, all the rest is mortal." It gives an eloquent synthesis of this work in which anatomy and art and philosophy are joined into a perfect and harmonious system. These figures have as a background an Italian landscape with flourishing trees and ruins of classic temples, and they appear to us as symbols of the new anatomy which has as a background the new life of the Renaissance and the ruins of classic science. The beautiful initials, conceived and delineated with a fine sense of art, give to the book a picturesque touch. Some years earlier, Gerolamo Fracastoro, a Paduan scholar, had published a magnificent poem in classic Latin verses, devoted to the story and pathology of syphilis, creating a medical text and an admirable work of poetry. Vesalius gave to anatomy its first textbook in a perfect artistic form. Both works are superb monuments of the scientific literature of the Renaissance.

The Fabrica was published on May 5, 1543 in a splendid edition which makes it also from the typographical point of view, one of the outstanding books of the 16th century. The question has often been asked why the Paduan professor had his book printed at Basle instead of Venice, where the supervision and the correction of the proofs would have been much easier and more convenient, and where he had already been closely connected with L. A. Giunta. But Venice and its printers and the Giuntas first of all, had at that time the reputation of having contributed to the spread of the Lutheran heresy, and in the year 1541, when the book was ready, the Diet of Regensburg had been convoked in order to stop Lutheranism, and the severe

persecution of the heretics had begun under the direction of the Society of Jesus. From northern Italy, many protestants had taken refuge in Switzerland. Basle was a town where Catholics and Protestants lived in peace. That Vesalius was aware of the danger which threatened him is proved by a passage in his *Epistle on Venesection*, published in 1539. "A very learned man, well satisfied because of his private wealth, was not ashamed to call Manardus, Fuchsius, Curtius and Brissotius, Lutherans in medicine, before a crowded assembly." These four physicians were all very well known to Vesalius and in close relation with him, and were at the same time suspected for their independent teachings.

In considering Vesalius' work, it is impossible not to refer also to Leonardo and his anatomical drawings, which make him appear to the impartial historian as the first anatomist in the modern sense of this word. The problem of the influence exerted by Leonardo on Vesalius has been often discussed, but a definitive solution is impossible. It is not even sure that Vesalius may have seen Leonardo's drawings, which seem to have been very little known at this time. But many facts allow us to admit that the great anatomist may have had at least some knowledge of this work, and of the fact that M. A. della Torre had intended to prepare with Leonardo's help, anatomical tables to improve the anatomical teaching. It is certain that Giorgio Vasari, historian and biographer of the great artists of his time, ascribing to this association the origin of Leonardo's anatomical drawings, told us a fact that was generally known. In any case, the revival of learning, the atmosphere of the Renaissance, the factors which had an impact on Leonardo's work inspired and encouraged the Paduan professor. But this does not diminish in any way the importance and originality of Vesalius' achievement.

Leonardo had started from a general conception of harmony and beauty which included the whole of the universe. He was a solitary thinker, driven to the study of all problems as an artist, a mathematician, and a philosopher. Vesalius, as a professor of surgery and anatomy, started from the real necessity for the physician and foremost for the surgeon, to know the anatomy of the body, and called for the help of an artist to accomplish this task. In the new conception of anatomy, free from the bonds of tradition and scholasticism, Leonardo was the precursor, but the conception expressed in a masterful form in his drawings found the convinced supporter, the systematic interpreter, and first of all, the great teacher, in Andreas Vesalius.

Leonardo's anatomical work was quite unknown to the scientific world, whereas the Fabrica caused an immense sensation, and the authority of Vesalius grew rapidly. He was invited to perform dissections at Pisa, where Cosimo, Duke of Florence, extended him a cordial welcome, ordered a corpse to be sent by special boat from Florence for the dissection, and offered Vesalius the chair of anatomy at the University. At Bologna he performed another public dissection and his friend Alvius, professor of anatomy, assisted him. At the same time, however, the learned Galenists understood the danger of this revolutionary trend, and the first alarm came from Paris, where Sylvius took upon himself the defense of Galen. He called upon Vesalius to renounce his heretical statements, to confess his mistakes, and to declare publicly his faults. As Vesalius answered that he had nothing to recant and that he stood for the truth of his assertions, Sylvius attacked his former pupil, declaring that he was not Vesalius but Vaesanus, a madman, and a two-legged ass; and his hatred went so far that as the most authoritative scholar of the Paris faculty, he wrote some years later to the Emperor Charles V, at whose court Vesalius was appointed, asking the Emperor that "Vesalius be heavily punished and in every way restrained, lest by his pestilent breath he poison the rest of Europe." On Vesalius' side stood his pupils, who loved and admired the teacher, but not all of them dared to take his part publicly, and some as Realdo Colombo were harsh in their criticisms. At the same time, a great number of plagiarists or "pirates," as Vesalius called them, in Germany, France, England and Spain, tried to present the work of Vesalius in changed form. Vesalius felt very deeply this animosity against him and especially the hostility of his teacher to whom he answered in a form no less violent than the one he had used. And perhaps he resented still more intensely the fact that the drawings had been copied or badly reproduced, the more as having spent large sums for them, he had nevertheless repeatedly stated that he was ready to put them without any charge at the disposal of any one who might wish to use them.

When finally, in 1544, as a young man of thirty, he decided to leave Padua and his chair, and to follow the apparently easier road, in line with the tradition of his family, accepting the call to become physician to Emperor Charles V, he broke with his past, burned his medical books and some manuscripts still unpublished.

Andreas Vesalius became the celebrated physician of Charles V and

of Philip I, the famous surgeon and consultant, but he never returned to his anatomical studies, to Padua, whence his enemies had driven him, just as the wars had once made living in Paris impossible for him. In all probability it was twenty years later the tyrannical regime of Philip II and his fight against the Low Countries, the independence of which was to be crushed at that time, that made his life at the Court of Madrid intolerable. After his resignation no more original contributions to anatomy, except the corrections to the second edition of the Fabrica (1555) were published by him. He well knew that his work as scientist and teacher had come to an end. But we have positive proof that he thought of it with deep nostalgia. In the letter to Gabriel Fallopius, his successor at Padua in answer to some objections raised by him, he wrote (1562): "I remember that very sweet life that was mine while I taught anatomy in Italy, the true nurse of genius. . . . No opportunity of a dissection can occur here, where I cannot have even a skull, but I still promise myself that on some favorable occasion I will thoroughly examine that true book of the human body, that is, man himself, and I will impart to you, in order to complete the art, any additional aspect which it will exhibit by virtue of its great abundance and of the singular skill of its Creator." And in another place: "I feel that the ornament of our art originates in that arena from which as a young man I was diverted to the mechanical practice of medicine, to numerous wars, to continuous travels. May you continue to embellish our common school the memory of which is always most dear to me."

The letter was published under the title Anatomicarum observationum Gabrielis Fallopii Examen in 1564, but this last work of Vesalius had a strange fate. Fallopio, to whom it was addressed and sent through the Venetian ambassador in Madrid, never received it, having died before its arrival. Vesalius, who arranged with the Venetian printer for its publication, never saw the volume, which was published at the time of his death.

But from the preface written by the publisher we learn that "before leaving for Jerusalem, Vesalius was greeted in the bookshop by Augustinue Gadaldinus, one of his warm friends and supporters, Andreas Marinus [the learned commentator of Rhazes] and some other prominent physicians," and that on the occasion the arrangements for the publication of the Examen were completed.

It may be that at that time the possibility of Vesalius' return to

the chair of Padua, had been taken into consideration, but we don't know anything about a formal offer of the Senate which, however, seems to have been likely, the chair having been vacant after Fallopio's death until 1565, when, after the news of Vesalius' death had reached Venice, Fabrizio d'Acquapendents, who was later Harvey's teacher, was appointed. Vesalius never returned from his unfortunate journey. But his great book shows him in the memorable aspect of the founder of anatomy as a science, as the professor at the medical school of Padua, the office he cherished most.

The creative activity of his life, his courageous fight against dogmatism, his great discoveries in the field of anatomy, the preparation of his books and the foundation of a new trend of medical thought evolved during the years of his teaching in Padua, the cradle of scientific Renaissance. In the history of the school of Fracastoro and Copernicus, of Galileo and of Harvey, Andreas Vesalius wrote one of the most glorious pages.

INTERMEDIARY METABOLISM INDIABETES MELLITUS

Harvey Lecture, January 15, 1942

WILLIAM C. STADIE

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The first was that of v. Mehring and Minkowski, who, by removal of the pancreas, first produced in experimental animals a condition closely resembling diabetes mellitus in man. The second was that of Banting and Best whose discovery of insulin made it possible to restore the diabetic animal to normal by the injection of a few milligrams of a highly purified protein. Around the first discovery there accumulated a great literature out of which there emerged a chemical picture of the disturbed metabolism of the diabetic. Out of the second there grew a problem, namely the problem of the chemical action of insulin. It proposes the questions: "By what chemical mechanisms does insulin produce its striking metabolic effects?" or "In what specific chemical reactions of the intermediary metabolism does insulin engage?" In contrast to the first field, the literature attempting to answer these questions is surprisingly small.

About three years ago I became interested in this latter problem. The experimental work^{1,2,3,4,5,6,7} which was then begun was done in collaboration with John A. Zapp, Jr., of the Department of Research Medicine, and Francis D. W. Lukens of the Cox Institute.* To them I wish to acknowledge my warm appreciation for their unstinting cooperation. In this paper I shall discuss some of these experiments. (It will be understood, of course, that limitation of space makes it impossible for me to mention many important and significant papers by other workers in this field.)

It seemed to me, however, that a direct attack upon the problem of

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chemical action of insulin was premature, for the interpretation of the general chemical picture of diabetes mellitus was still a matter of sharp dispute. Students of the disease were divided in advocating two contending theories of diabetes. On the one side we find the under-utilizationists. They constitute the large majority and their thesis is the more popular one. It holds that the main, if not the sole, defect in the intermediary metabolism in diabetes mellitus is one in which the peripheral tissue (i.e., chiefly muscle) cannot, either at all or in sufficient measure, oxidize carbohydrate without the catalytic intervention of insulin. On the other side is a smaller group—the over-productionists. Their thesis is that there is an overproduction of carbohydrate by the liver chiefly from fatty acids which are convertible into carbohydrate. The function of insulin is to control, directly or indirectly, the extent of this conversion; its action in the periphery to catalyze the oxidation of carbohydrate, is either nil or of minor importance.

In the light of either theory the complete diabetic is in a bad way. According to the under-utilizationists no energy is derivable from carbohydrates; about 60 to 80 per cent of that from protein is lost, hence fat must form the bulk of his metabolic mixture. According to the over-productionists the diabetic is wasting potential foodstuffs by excreting large amounts of fat in the form of sugar into the urine. In either case the question of fat metabolism assumes major proportions and until we are well oriented on this question the problem of the chemical action of insulin must remain obscure. It is necessary then to examine the hypothesis of fat metabolism which grew up simultaneously with the development of the above hypotheses of the diabetic defect.

In the light of our present knowledge of fat metabolism it is possible, I believe, to include all conceivable hypotheses of fat metabolism in the two following chemical mechanisms (Fig. 1):

Fig. 1—Conceivable chemical mechanisms of fat metabolism:

I—Direct utilization by peripheral tissues.
Oxidation is both initiated and completed in the periphery.

II—Indirect utilization.
Preliminary partial oxidation in liver to diffusible, oxidizable substances which are utilized by the periphery.

I shall discuss later reasons for believing that both of these mechanisms are operative at the same time.

Concerning the first mechanism, that is, the direct utilization of fat

in the periphery, almost nothing is known. The literature contains few experiments which shed light upon the mechanisms involved. In sharp contrast, we find the intermediary metabolism of carbohydrates by the muscle to be fairly well mapped out; yet a similar map of the intermediary metabolism of fat in the muscles is virtually blank.

Concerning the second mechanism, i.e., the preliminary partial oxidation of fats in the liver, we are more fortunate, and indeed it is this mechanism which I shall chiefly discuss tonight. It is here, however, that differences of opinion arose and split the diabetic camp into two. The details of the contending hypotheses which have been advocated are summed up in Fig. 2.

Fig. 2—Contending hypotheses concerning the preliminary oxidation of fatty acids in the liver:

II-A. Fatty acids oxidized to ketone bodies + acetic acid.

II-B. Fatty acids oxidized to ketone bodies + glucose.

II-C. Fatty acids oxidized to ketone bodies only.

According to the first of these, II-A, fats undergo a preliminary partial oxidation in the liver to a four carbon ketone residue, the balance of the molecule being oxidized to a two-carbon compound, i.e., acetic acid. In the normal both of these substances are freely oxidized in the periphery, but in the diabetic, the oxidation of the ketone residue cannot occur. This represented the position of the under-utilizationists.

According to the second hypothesis, II-B, fatty acid likewise undergoes partial oxidation in the liver but the products of this oxidation are glucose and ketone bodies. This was the contention of the over-productionists.

The third hypothesis, II-C, postulates that the partial oxidation of the fatty acids in the liver results in the formation of ketone bodies only. This position represents, indeed, a new departure and is the one for which experimental evidence will be given.

It is interesting to note the influences which focused attention upon the first of these hypotheses and obscured the others. Among these were: first, the ascendency of the under-utilizationists led by Lusk; second, the entrenched position of the Knoop hypothesis of successive beta oxidation of fatty acids so strongly advocated by Embden and by Dakin; and lastly, the development by Woodyatt and by Shaffer of the hypothesis of obligatory coupling of ketone-body-carbohydrate oxida-

tion in the periphery. It became necessary to examine these last two hypotheses before proceeding further.

Fig. 3-Current hypotheses of fat metabolism in the diabetic:

I-Knoop hypothesis of successive beta oxidation.

Long carbon chains of fatty acids oxidized two carbons at a time with formation of acetic acid+one ketone molecule per molecule of fatty acid.

E.g. Palmitic+6.5 O2=1 ketone+6 acetic.

II-Ketones oxidized only by obligatory coupling with carbohydrate oxidation.

III-Fat converted to carbohydrate by liver.

Knoop's original experiments with phenyl substituted fatty acids showed from the nature of the phenyl residue excreted in the urine, that the short fatty acids which he used were oxidized at the carbon atom which is in the beta position to the terminal carboxyl group. In the case of the five carbon fatty acid, the longest chain used, Knoop found delta as well as beta oxidation. He made no statement about the possible splitting off of a two carbon compound such as acetic acid, nor did he conclude that this beta oxidation found with short fatty acids was representative of a general biological reaction applicable to all fatty acids. These experiments of Knoop were rapidly confirmed and extended notably by Dakin⁸ and the experience with short fatty acids was generalized to include a biochemical reaction for the oxidation of all fatty acids. There were two characteristics of this oxidative reaction, namely, (1) oxidation at the carbon atom next but one to the terminal carboxyl group, i.e., beta oxidation, and (2) the splitting off of two carbon atoms presumably as acetic acid. The process became known by its full name, successive beta oxidation, and as such became firmly fixed in the literature. According to it the oxidation of the long naturally occurring even numbered fatty acid chains containing sixteen or more carbon atoms would proceed as follows: Successive molecules of acetic acid would be split off by beta oxidation leaving a series of fatty acid residues each shorter by two carbon atoms than its immediate precursor. Finally one molecule of butyric acid would result which in turn was oxidized to aceto-acetic or beta hydroxy-butyric acid. For every molecule of fatty acid oxidized only one molecule of ketone-body would be formed. This process was confined to the liver; there is no evidence that a similar process occurs in the periphery.

Along with the hypothesis of successive beta oxidation, another

hypothesis concerning fat metabolism was developing. I have called this the hypothesis of obligatory coupling of ketone-carbohydrate oxidation. According to it there is a definite stoichimetric reaction between ketone and carbohydrate of such a nature that exactly one, or perhaps two, molecules of ketone reacts with one molecule of carbohydrate in such a way that when the carbohydrate is oxidized the ketone is simultaneously oxidized. If this coupled reaction cannot take place either by lack of available carbohydrates, as in fasting, or lack of ability to oxidize carbohydrate, as in diabetes, then there is no way in which the ketone bodies can be oxidized and they accumulate or are excreted as toxic or waste products of fat metabolism.

The combination of these two hypotheses represented in the main the position of the under-utilizationists. The complete diabetic losing most of the energy from protein and carbohydrate still has 50 per cent of the original energy of the fat in the form of acetic acid. Lacking ability to bring into play the obligatory coupled reaction with carbohydrate the diabetic excreted the residual ketone. To be sure, this was a bit wasteful of fat but unless the ketones were toxic, which most people agreed was not the case, the process would have been harmless were it not for the unfortunate fact that ketone excretion robbed the body of base, thus threatening fatal coma. Further, the hypotheses avoided postulating the formation of carbohydrate from fat. Finally, the discovery of the ketogenic-antiketogenic ratio appeared to offer a quantitative explanation of the marked influence of carbohydrate utilization upon ketone excretion. There even accrued about this position a supporting aphorism: "The fats burn in the flame of the carbohydrates."

Meanwhile the position of the over-productionists was developing, but upon somewhat less well-entrenched lines. Obviously they could hardly espouse the obligatory coupling hypothesis for then ketonuria would never occur since by assumption abundance of carbohydrate is oxidized in the periphery. They therefore occupied themselves with undermining this position of the under-utilizationists, and showed, by the work of Chaikoff and Soskin,⁹ for example that the ketone bodies were oxidized in the periphery without coupling with carbohydrate oxidation. The abnormal fat metabolism in diabetes could be more easily explained by postulating that there occurred in the liver the following reaction:

Fatty acid + oxygen = ketone bodies + glucone

The exact stoichiometrical relations of this reaction were never clearly defined. The important assumption was made that this reaction was controlled by insulin. In diabetes the control was lost and the reaction ran to excess with overproduction of both ketone bodies and glucose.

The possibility of the conversion of fat to carbohydrate continued to be fought for bitterly by its advocates but their arguments brought little conviction to the under-utilizationists. Indeed, Lusk characterized the reaction as a "figment of the imagination" which "should be relegated to the realm of scientific superstition." However, the critical experiment which would decide the matter one way or another still remained to be done.

It seemed to me that the problem of the chemical action of insulin must be preceded by a flank attack upon the problem of fat metabolism in diabetes. Indeed, in retrospect of the literature, it was evident that the position held for a period of 30 to 40 years was already considerably undermined. For example, in the normal fasting animal or in the diabetic animal, who must be subsisting chiefly upon fats, there should be found in the liver large amounts of intermediate fatty acids with 14, 12, 10 or less carbon atoms. But they had never been found.

Again, consider the case of the working diabetic, particularly the exercising depancreatized dog. He should oxidize no carbohydrate, hence he could oxidize no ketones. Now exercise him and measure the extra calories produced. These extra calories must come from fat, and by the Knoop hypothesis, one could calculate exactly the extra ketones formed. These should all appear in the urine, but no extra ketones whatever were found, as can be easily calculated from Barker's recent experiments. The implication seems obvious: The extra fat was completely oxidized without benefit of coupled carbohydrate oxidation. This fact, namely, that exercise did not increase the ketonuria of the complete diabetic, was completely at variance with the obligatory coupling hypothesis and should long ago have forced its abandonment.

The generalization of Knoop's experiments on short fatty acid chains to include an explanation of fat metabolism in the diabetic came under fire shortly after its publication. In 1916 Hurtley, 11 an English clinician, published a comprehensive paper on ketosis in diabetics. He was struck by the fact that none of the lower fatty acids had been found in the livers of patients dying in coma. Particularly was this so in the case of butyric acid which should have been revealed by its odor



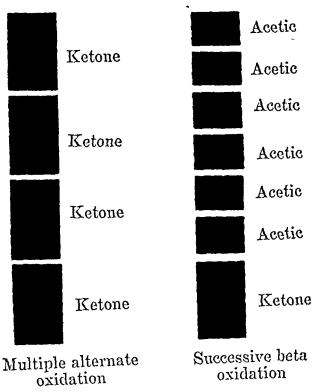


Figure 4

alone. Hurtley had no experiments but on theoretical grounds he proposed an alternative hypothesis, which became known as the multiple alternate oxidation hypothesis. On the basis of in vitro studies with liver slices Jowett and Quastel¹² brought it out again. The two hypotheses are contrasted in a schematic way in Figure 4. The multiple alternate oxidation hypothesis states that the long fatty acid molecule is oxidized along the entire length of the chain at alternate carbon atoms. The result is the complete disappearance of the fatty acid with the simultaneous appearance of an equivalent amount of ketone bodies. The Knoop hypothesis, on the other hand, supposes that there is a step by step oxidation of the molecule. Paired carbon atoms are split off to form acetic acid leaving a residue of one molecule of ketone body. The contrasting chemical consequences of these two theories for the oxidation of palmitic acid, for example, are as follows: (1) The production of one molecule of ketone should require 1½ molecules of oxygen or 6½; (2) for

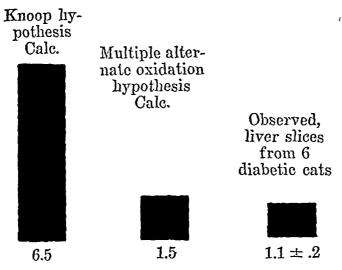


Fig. 5—The oxygen requirements (moles) for the production of a mole of ketone from palmitic acid by hepatic oxidation.

every molecule of fatty acid oxidized there should appear 4 molecules or only 1; (3) the oxidation of one molecule of fatty acid should give no acetic acid or 6 molecules. In our own experiments we attacked the problem in three different ways each of which was designed to give a critical answer to the problem. In the first of these, illustrated in Figure 5, the oxygen requirements for the production of one mole of kerone body are given. For the multiple alternate oxidation hypothesis there would be required 1.5 while for the Knoop hypothesis the value would be 6.5. The answer to the problem should be found in the fat metabolism of the liver from the diabetic cat. This was measured in the following way: Two to four days after pancreatectomy, the animal was sacrificed, and liver slices were prepared and equilibrated in vitro in suitable buffers with 100 per cent of oxygen. Ketone formation and oxygen consumption were measured over a period of two hours. The results appear in the last column. We found (Fig. 6) in a series of six diabetic cats a ratio of oxygen consumption to ketone formation of 1.1 ± 0.2 a value not significantly different from that required by the multiple alternate oxidation hypothesis. The ratio clearly excludes the Knoop hypothesis. In the second type of experiment (Fig. 6) we looked for the possible formation of acetic acid. These liver slices from diabetic cats were producing large amounts of ketone bodies in vitro as shown by the top block. The calculated acetic acid according to the Knoop hypothesis is indicated in the solid block. Yet in a series of animals Non-formation of Acetic Acid by Liver Slices from Diabetic Cat (No. 106B).

Observed hepatic ketones

Acetic acid formation by Knoop hypothesis 0.0 Observed acetic acid formation 0.0 Observed lower fatty acid (C_2-C_8) ,

Fig. 6

The Balance between Fatty Acids Oxidized and Ketones Formed by the Liver.

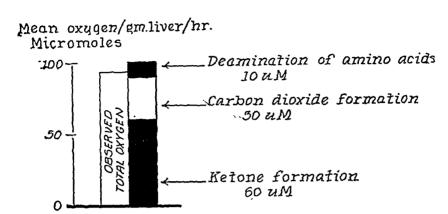
(Diabetic cats; phlorhizinized cats or rats.)

| FATTY ACID OXIDIZED . |
|--|
| Ketones by Knoop hypothesis |
| Ketones by multiple alternate oxidation hypothesis |
| Ketones observed |

Fig. 7

we were unable to demonstrate any acetic acid either initially or at the end of two hours of equilibration in vitro. The possibility that the acetic acid was formed and then oxidized, was excluded by the determination of the respiratory quotient of the slices which in that case should have been about 0.7 instead of the value of 0.3 which was actually found. We also searched for the possible formation of the intermediary fatty acids containing one to eight carbon atoms which were supposed to form by successive beta oxidation but were unable to demonstrate even traces of them. The third type of experiment (Fig. 7) is in essence a

The Oxidative Metabolism of Liver Slices from Six Diabetic Cats.



F16. 8

balance study of the fatty acid metabolism of liver slices from diabetic, normal phlorhizinized cats, and phlorhizinized rats. We would expect, according to the multiple alternate oxidation hypothesis that for every mole of fatty acid which is completely oxidized and therefore disappears from the liver, there would be formed four moles of ketones. That is to say, the fatty acid oxidized away should be replaced, as the slide shows, in the first and third blocks, by an equivalent amount of ketones. On the other hand, the Knoop hypothesis would predict the formation of only one-fourth equivalents of ketones. In a series of eight animals we found as the last segment of the slide shows, that the decrease by oxidation of fatty acid during two hour equilibration of the liver slices in vitro was accounted for by the appearance of approximately, an equivalent amount of ketone, a result in accordance with the multiple alternate oxidation hypothesis.

This conclusion must not be interpreted as meaning that beta oxidation does not occur at all in the liver. Indeed, Stetten and Schoenheimer¹³ using deuterium have definitely shown that it does occur. It does mean, however, that the great bulk of fatty acid oxidation in the liver goes by way of multiple alternate oxidation rather than beta oxidation.

It is now possible to write the stoichiometrical equation for the oxidation of fatty acids in the liver of the diabetic and it is to be noted

that no glucose is included in the reaction. However, the problem is of sufficient importance to warrant further experiment and I show two other types of evidence on this point. Glucose is comparatively rich in oxygen, namely, one atom of oxygen per atom of carbon. Fatty acids on the contrary contain very little, about 1/8 of an atom per atom of carbon. If the diabetic liver converts fatty acids into glucose it must furnish by respiration at least % of an atom of oxygen for every atom of fat carbon which it builds into the glucose molecule. Hence a balance sheet of the oxidative metabolism of liver slices from diabetic cats should yield significant information about the possibility of the conversion of fats to carbohydrates. Such a balance sheet was determined in the case of six depancreatized cats and is shown in the slide. Three known oxidative processes were independently measured and the oxygen required for each calculated (Fig. 8). Deamination of amino acids measured by urea formation required 10 µM of O2 per gm. of liver per hour. Carbon dioxide formation required 30, and ketone formation required 60. The sum of these is 100 µM/gm. of liver/hr. The total actually observed oxygen uptake was 88 µM/gm. of liver/hr. not significantly different from the sum for the three known oxidative processes. In other words, within the limits of error, the balance was exact. But these same cats excreted, 1 to 4 hours before the experiment with the liver slices, amounts of glucose which if it came from fat would have required at least 97 µM/gm./hr. for this one oxidative process alone. But the experiment shows that there was no oxygen whatever available in the metabolism of the liver slices for this supposed synthesis. This experiment, alone, even if there were no others available, is strong proof that the conversion of fatty acids to glucose does not occur in the diabetic liver.

In the second type of experiment bearing on this point (Fig. 9), we measured the actual new carbohydrate formation by diabetic liver slices equilibrated in vitro. In addition we measured the protein metabolism by measuring urea formation and the fat metabolism (as ketone formation) in order to know how much glycerol might be available for carbohydrate formation. And lastly, we measured lactic acid metabolism in order to know its role in potential carbohydrate formation. In this way we could construct a balance sheet of carbohydrate precursors. These liver slices were actively oxidizing fats as shown by the abundant ketone formation and according to the hypothesis should also have been forming new carbohydrate from fat. But when the balance sheet was

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Synthesis of Formentable Carbohydrate by Liver Slices from Diabotic Cats
Equilibration for 2.0 hours at 38°; average sample 200 to 250 mg.; buffer 3.0 cc. of phosphate-saline or bicarbonate-saline at pH 7.2.
Supplements as indicated.

The results are expressed in micromoles or microequivalents per gm. per 2 hours.

| Cat. No. | Supplement | Oxygen | л. Q. | Increase of ketone bodies | Increase of urea + NII, | Change in lactic acid | Increase of total carbo- hydrate | Increase of total carbo- hydrate corrected | Type of correc- tion* |
|----------------|---------------------------------|--------|-------|------------------------------|--|--------------------------------|---|--|-----------------------------|
| | | Micro- | | micro- | micro- equiva- | micro- | micro- | micro- | |
| | | mores | | 6310111 | lents | 550 | 2300 | 6316111 | |
| 107CT | None | 177 | 0.34 | 59 | 95 | 12.0 | 61.0 | 3.6 | N, K, L |
| $110\Lambda U$ | 3 | 311* | 0.32 | 170 | | | 15.5 | 1.5 | |
| HIEU | 3 | 167 | 0.35 | | 21 | 15.3 | 10.3 | 11.0 | 77 " |
| HIFU | 3 | 185 | 0.33 | | | 17.9 | 9.9 | 11.9 | ;; ;; |
| 120BU | * | 185 | 0.37 | 50 | = | 16.2 | 6.9 | 6.1 | " K. L |
| 120BT | * | 159 | 0.38 | 07 | = | 3.0 | 1.7 | 1.2 | |
| UVIII | 0.0005 of d-lactate | | 0.45 | Si | | 0.4 | 30.0 | 20.1 |)))) i) |
| HIBU | 0.0025 " " | 191 | 0.39 | 22 | | 0.81 | 15.0 | 1.5 | " |
| 111CU | | 123 | | | £ | 0.01 | 27.0 | 0.1 | " |
| UGIII | " " 100.00 | 500 | 0.53 | | 81 | 780 | 51.0 | 8.1 | 3 |
| Mean . | | | : | | 82 | | | | |
| , | | | গ্র | Equilibrated 1 hrs. | rs. Summary | | | | |
| | | | Š | Samples | Type of correction | Mean | corrected ca | Mean corrected carbohydrate formation | ormation |
| | | | | 12 | N, K, L | 1.6 ± 1.3 | E.1 | | |
| | | | | | 7 | 78 # 28 | 8: | | |
| | | | · | | " K | 5. | | | |
| | | | 1 | 10 | Mran of all | 11 41 12 12 | 2.3 = 1.0 = 0 | 56 ± 25 = 1.0 ± 05 mg per gm. per 2 hrs. | i. per 2 hrs. |
| + 1 fath. | Market of commention without in | 1 | 1 | aution for oliver | the tout. V - meanation for alreadenic united to correction of already from ful calulations. | 1, - 00, 1 | sala of ales | the tribution of | catabalized. |

* Method of correction given in the text: N = correction for glycogenic amino acids; K = correction of glycerol from fat catabolized; L = correction for increase or decrease of lactic acid.

added up we could find no significant amount of new carbohydrate formation by the liver slices from the diabetic cats which could not be accounted for as coming from either catabolic protein, catabolic glycerol or lactic acid initially present in the liver.

In contrast to our inability to demonstrate formation of glucose from fat was our experience with a known precursor of carbohydrate. For example, these same liver preparations in the presence of lactic acid formed new carbohydrate up to 10 mg./gm. of liver/2 hrs. an amount sufficient to account for a large fraction of the glucose actually excreted by the cat in a preliminary period of observation.

These experiments convinced us that the diabetic liver was producing nothing but ketones by partial oxidation of fatty acids. Neither acetic acid nor glucose was formed. It seemed clear that these ketone bodies must be oxidized in the periphery for otherwise there would be practically no source of energy available since most of the energy from protein and all of that from carbohydrate was out of the picture. The demonstration that the diabetic could utilize ketones peripherally became important and in five ways we showed that this was the case. Four of these were on animals and one on human cases of diabetes mellitus. I shall mention only two types of animal experiments.

In a preliminary period of 2 to 3 hours the urinary ketone excretion of diabetic cats was measured (Fig. 10). The animal was then sacrificed, the liver quickly removed and slices were prepared and equilibrated in suitable buffers at 38° C. for a period of 2 hours. The slices and the medium were then analyzed for ketone bodies and the amount of ketones formed by the liver calculated to body weight per hour. The figure (Fig. 10) shows that the total ketone formation by the liver was greatly in excess of the preliminarily determined ketone excretion. The difference can only represent the ketone body utilization by the peripheral tissues, chiefly muscle, of the intact diabetic cat. The mean value in the case of eight diabetic cats was 1100 M/kg. of body weight/hr. which is equivalent to 2.3 gm. of fat/kg./day.

The second method stands in contrast to the other methods used in which surviving liver slices or muscle minces were equilibrated in vitro. Possible objections to such preparations were avoided by using the intact diabetic cat. First the urinary ketone excretion was measured over a preliminary period of 2 to 4 hours. Then the abdomen was opened and with as little trauma as possible samples of portal and hepatic blood

METHOD I. KETONE UTILIZATION BY 8 DEPANCREATIZED CATS.

KETONES FORMED BY LIVER SLICES

Per Kg body weight per hour

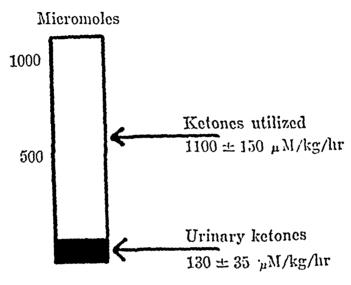
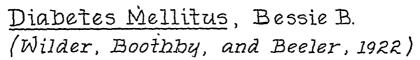


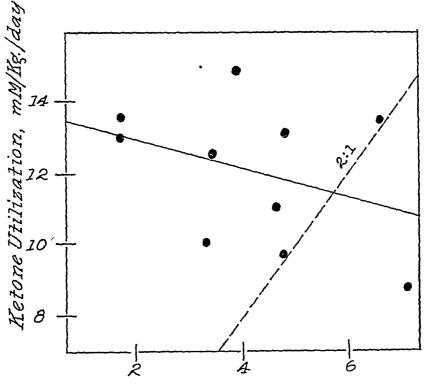
Figure 10

Fig. 10A—Ketone Formation by Liver of Diabetic Cate, Calculated from Portal and Hepatic Blood Ketone Concentration in Intact Animal

| Cat. No. | Blood ketones, micromoles per cc. | | Calculated liver ketone formation, micromoles |
|--------------------|--------------------------------------|----------------------|---|
| | Portal | Hepatic | per kilo cat per hour |
| 96D 96E 102A | 9.4 16.4 9.7 | 10,5 17,7 11,7 | 875 1000 1910 |
| Mean | } | | 1265 ± 110 |

were obtained and their ketone bodies determined. In all cases, the outgoing hepatic concentration was higher than the ingoing portal ketone concentration. In order to calculate the total ketone production by the liver we used a mean value for liver blood flow taken from the literature (Schmid).¹⁴ The ketone body production by the liver so calculated was again greatly in excess of the ketone body excretion determined during the preliminary period. The difference is utilization. The





"Antiketones" oxidized, mM/Kg/dau

Fig. 11

results (equivalent to 2.2 gm. of fat/kg./day) are in agreement with our three types of in vitro experiments in showing a marked utilization of ketone bodies by the peripheral tissues of the diabetic cat.

On the basis of these experiments and other evidence it seemed reasonable to us to exclude the overproduction hypothesis as an explanation of the diabetic defect and adhere to the underutilization hypothesis. The diabetic in calling for reserves of energy from fat, could partially oxidize the fatty acids in the liver to ketone bodies which could be freely used in the periphery without insulin and without the necessity of coupling this oxidation with the oxidation of carbohydrates.

But there still remained two things to be done. The first was to obtain evidence for the oxidation of kerones by the peripheral tissues in human cases of diabetes mellitus, and the second was to re-examine the so-called ketogenic-antiketogenic ratio which still represented in the

literature the expression of the obligatory coupling hypothesis in the human diabetic.

The hypothesis states that antiketogenic in the human subject is based upon a ketolytic reaction in the body between acetoacetic acid, the first formed of the acetone bodies, and a derivative of glucose (or other antiketogenic substance), the compound being further oxidized but that failing to react with ketolytic substance, acetoacetic acid is resistant to oxidation, accumulated and is . . . excreted. . . . The fact that one finds at the threshold of ketosis an approximately constant ratio between the number of molecules of the precursors of acetoacetic acid and of glucose in the metabolic mixture, must mean that the further oxidation of acetoacetic acid constantly taking place under normal conditions is accomplished through a chemical reaction with a derivative of glucose. . . ."

Fortunately, there is in the literature a sufficient amount of the necessary data for re-testing this hypothesis in subjects with diabetes mellitus. The cases are all classical ones, reported in the literature before the advent of insulin when marked ketonuria was, of necessity, a frequent accompaniment of the disease. Similar data on human diabetics will in all probability never be obtained again, since it is unlikely that patients with marked ketonuria will be allowed to remain untreated over long periods of time. The data include calorimetric measurements of the metabolic mixture of proteins, fats and carbohydrates together with the total ketone body excretion. Hence it is possible to calculate the total carbohydrate or so-called antiketones oxidized. In addition, from the total fat catabolized and the urinary ketone excretion, it is possible to calculate the total fat utilized or its equivalent in ketones. The best way to examine the data is to put it in the form of an equation and apply the data to the equation by statistical methods. When there is a definite excess of ketone excretion the equation is a simple one and is shown in the slide (Fig. 11) by the dotted straight line labelled 2:1. The equation : merely restates the hypothesis, namely, that two molecules of kerones but no more, are oxidized for every mole of antiketones oxidized. The figure shows the data in one case, that of Bessie B. of Wilder, Boothby and Beeler,16 one of the best studied cases of the series. The ordinate shows the mM of ketone utilization calculated from the metabolic mixture. The abscissa shows the mM of antiketones oxidized. If there were

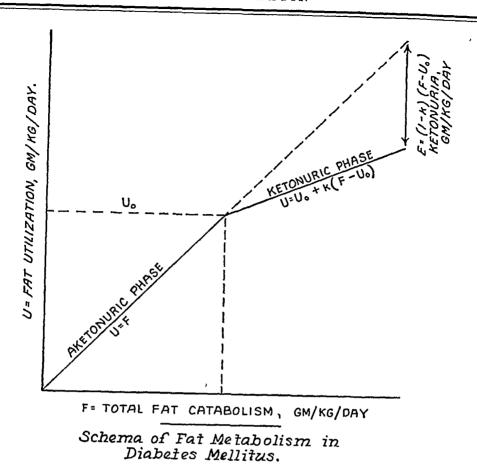


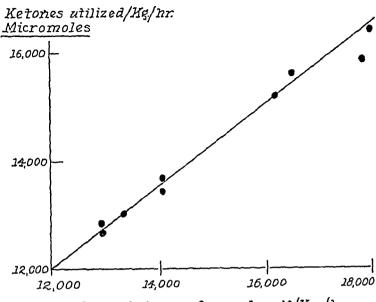
Fig. 12

anything in the obligatory coupling hypothesis the observed points should fall on the line marked 2:1 which is calculated for a 2:1 ketogenic-antiketogenic ratio. But the true line for the data runs in the opposite direction with no relation whatever to the theory. Moreover it is important to note that the intercept constant, when antiketones were zero, is about 14 and is very greatly in excess of zero which it should be according to the theory. That is to say, Bessie B. was utilizing either ketones or fat even in the practically complete absence of carbohydrate oxidation, a conclusion in conformity with the experiments with the diabetic cats and opposed to the obligatory coupling hypothesis. Analysis of five other cases of diabetes mellitus for which complete data were available in the literature all showed the same thing as did this illustrative case. There was found no significant correlation between antiketones and fats oxidized. It seemed to us from this analysis that the last remnant of the obligatory coupling hypothesis has vanished for there was no suggestion in the data that there was any fixed molecular ketogenic-antiketogenic ratio. On the other hand, there were strong indications that these patients, many of whom were almost complete diabetics, were like our diabetic cats, completely oxidizing ketones or fats without simultaneous oxidation of carbohydrates.

It was found possible to state a simple hypothesis of fat metabolism in diabetes mellitus which would conform to the observations in these clinical cases and with the experiments with animals. It is as follows: Up to a certain level all fat catabolized is completely oxidized; hence there is no ketonuria. Beyond this level all fat catabolized is not completely oxidized; hence part of the fat catabolized is excreted unburned in the form of ketone bodies. The action of carbohydrates is simply to spare fat oxidation; there is no molecular reaction, hence there is no molecular ratio between the two.

The diagram (Fig. 12) shows the implications of this hypothesis. The figure shows the amount of fat in the metabolic mixture. On the abscissa F is the total fat catabolized, that is, the fat poured into the stream of intermediary metabolism and undergoing oxidations of one sort or another. On the ordinate is shown by U the total fat which is completely oxidized. Both of these values are in gm./kg./day. There are two phases in the metabolism of fat, the aketonuric and the ketonuric phases. Starting from zero and increasing the amount of fat catabolized, we pass through the aketonuric phase along the line marked U=F. Here all of the fat in the metabolic stream is completely utilized and there is no ketonuria. But, at any given state of activity, the ability of the organism to mobilize exactly that amount of fat which can be completely oxidized appears to be limited. This upper limit is shown by the dotted line marked Uo. I call this the maximal aketonuric fat utilization. If the call for fat calories exceeds this aketonuric level, it is answered in the following way: Extra fat is catabolized above the aketonuric level, but only part of this extra fat is completely oxidized. This is shown by the bending of the line marked ketonuric phase away from the extended dotted line which would represent complete oxidation. The difference between these two lines, indicated by the double arrow on the right, is not utilized and hence is excreted in the form of the ketone bodies. In other words, the diabetic can only increase his energy from far above the basal aketonuric level by wasting part of the far catabolized by the excretion of ketone bodies combined with base at the risk of acidosis.

Diabetes Mellitus. No. 740. Joslin, 1915.



I.- Total ketones formed, uM/Kg./hr.

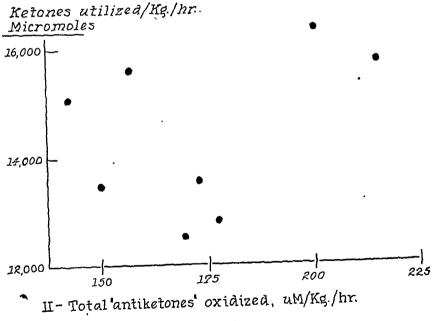
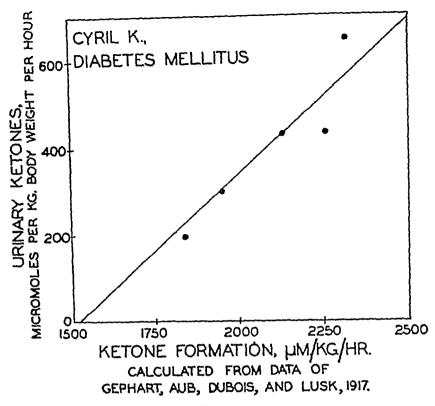


Fig. 13

This hypothesis can be tested by applying the data of diabetic cases in the ketonuric phase. There should be found, as indicated in the diagram, a straight line relation between the fats completely oxidized and the total fat catabolized. When this line is extended back to the point where there is no ketonuria, the value of the aketonuric fat utilization



F16. 11

is obtained and this should be about the same value for all cases. In other words, if we plot the data obtained from a diabetic during ketonuria, we should obtain a line similar to the one marked "ketonuric phase" in the slide.

I show (Fig. 13) one representative case, No. 740 of Joslin.¹⁷ The data represent as before the metabolic mixture determined by calorimetric methods. For contrast the diagram shows on the left the present hypothesis and on the right the ketogenic-antiketogenic hypothesis. On the left the total fat catabolized calculated as ketone bodies is plotted against the total fat completely utilized: The observations fall about a straight line as expected from the hypothesis. At 1200 µM/kg./hr. of ketone equivalent to 2.1 gm. of fat/kg./day, catabolism and utilization are equal, hence there is no ketonuria and 2.1 is the aketonuric fat utilization in this case. When ketones formed were 1800 µM only 1600 µM were utilized. In other words, about 200 µM or ½ of the fat catabolized was excreted as ketones. In the segment on the right of the slide the data from the same case are plotted according to the ketogenic-antiketogenic hypothesis. Here, as in the cases hitherto illustrated, there is no correla-

Fig. 15
Summary of Maximal Basal Aketonuric Fat Utilization in Cases of Diabetes Mellitus

| Case | Reference | Maximal aketonuric fat utilization in equivalents of ketone bodies |
|---|---|---|
| Group I Cyril K. | Gephart, Aub, DuBois and | mM. per kgm. per day |
| Bessie B. Kramer 740 E. W. Jervis B. | Lusk ¹⁸ Wilder, Boothy and Beeler ¹⁵ Shaffer ¹⁵ Joslin ¹⁷ Mosenthal and Lewis ¹⁹ Richardson and Ladd | 35 34 35 28 (47)* |
| Group II | | } |
| Ray H. Chris. Q. Harold J. George H. Frank B. K. A. | Richardson and Ladd McClelland, Spencer, and Falk | 37 26 37 37 37 37 |
| | Mean *(11 cases) Equivalent in grams of fat | 34 ± 1.6 (S. E. of mean) 2.5 ± 0.12 |

^{*} Excluded from basal mean on account of fever (102° F.).

tion between the data and the hypothesis.

I have preferred to talk about utilization in order to emphasize the question of fat oxidation in the diabetic, but the hypothesis could just as well be framed in terms of urinary ketone excretion. By way of illustration I show the data in the case of Cyril K. of Gephart, Aub, DuBois and Lusk¹⁸ (Fig. 14). Total fat metabolism is expressed in ketone equivalents as μ M/kg./hr. and the urinary ketone in the same units. The data fall about a straight line as expected from the hypothesis. Note that when the urinary ketones are zero, fat catabolism is equivalent to 1500 μ M/kg./hr. or about 150 gm. of fat per day. This was Cyril K's basal aketonuric fat utilization value. Note further that when he increased his fat catabolism by 1000 μ M he excreted about 600 μ M out of this extra 1000. In other words, Cyril K. could only use about 40 per cent of the fat catabolized above his basal aketonuric fat utilization level.

All cases for which there were data available in the literature (Fig. 15) showed the same relations as those shown in these illustrative cases.

The analysis of these cases is shown in this slide. There are twelve cases. The values for the aketonuric fat utilization are shown in the last column. With the exception of Mosenthal and Lewis'10 case E. W. which was the only case with infection and fever, these values are all concordant and the mean value is equivalent to 2.5 gm. of fat/kg./day. The findings here outlined are offered as proof that the hypothesis of fat metabolism in the diabetic stated previously is in conformity with the quantitative experimental and clinical data available for testing it.

One more point relating to fat metabolism remains to be discussed. There are two possible types of fat metabolism. The first is the direct oxidation of fat both initiated and completed in the peripheral tissues. Almost nothing is known about the chemical reactions or enzymes involved in this type except that it appears never to give rise to ketonemia. The second is the indirect type in which fat oxidation is initiated in the liver by the sole formation of ketones and completed in the periphery by the subsequent oxidation of these ketones. There are reasons for believing that both of these types are operative at the same time. For example, we found with liver slices from diabetic cats a maximum ketone formation equivalent to 2.3 gm. of fat per kg./day. Practically all of this was utilized. But the total basal metabolism of the diabetic cat, according to Ring and Hampel²⁰ is equivalent to about 8 gm. of fat/kg./day. That is to say, only 30 per cent of the total fat metabolism could be accounted for by the mechanism of indirect fat oxidation. Recently Crandall, Ivy and Ehni21 using London cannulae, came to the same conclusion in the case of normal fasting dogs. They could only account for about 50 per cent of the total fat metabolism by hepatic ketogenesis. A second reason for believing in the dual mechanism of fat oxidation is found in a consideration of the oxygen requirements of the liver. If all of fat metabolism went through preliminary ketone formation by the liver, the amounts of oxygen required would be very greatly in excess of the values which are actually found for the oxygen consumption of that organ. Thirdly, diabetic muscle, when equilibrated in vitro, shows a respiratory quotient of 0.7, indicating an ability on the part of the muscle to oxidize fats directly.

The results of our experiments together with related evidence in the literature may be summed up as follows:

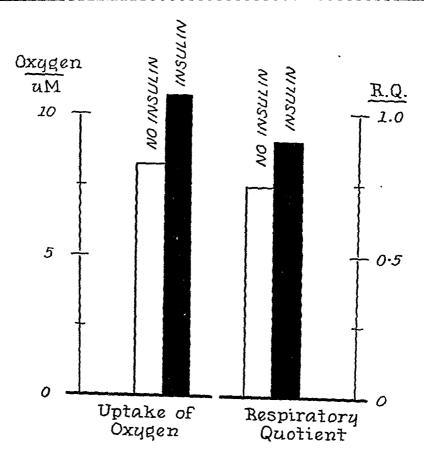
The diabetic who by reason of insulin lack is unable to utilize carbohydrates to the full measure of his metabolic needs, must fall back upon fat for his energy requirements. Part of this need is met by the complete oxidation of fat in the muscles themselves. However, a considerable fraction, estimated as ½ to ½ of the total caloric needs from fat, is obtained by a preliminary oxidation of fats in the liver to ketone bodies only. Neither acetic acid nor glucose are formed by this oxidation. These hepatic ketone bodies are freely utilized for energy by the periphery without insulin and without the necessity of simultaneous carbohydrate oxidation. This reserve mechanism, however, appears to be incapable of fine regulation so that when the demand for fat calories exceeds a certain level, approximately 2.5 gm. of fat/kg./day for the resting state, ketone bodies in excess of needs are formed by the liver. The excess is excreted in the urine. If this excessive fat catabolism continues unchecked ketosis and coma follow.

SPECIFIC CHEMICAL ACTION OF INSULIN

In the time remaining at my disposal I shall discuss some of the evidence in the literature together with experiments of our own which bear on the problem of the specific chemical action of insulin upon the processes of intermediary metabolism. Initially it is necessary to admit that the summation of this évidence is far from giving a satisfactory answer to this problem. Nevertheless certain conclusions although of a tentative nature can be drawn.

First, however, may be discussed what might be called the physical hypothesis of the action of insulin. This hypothesis holds that the chemical reactions within the cell by which carbohydrate is oxidized are independent of insulin, but that ordinarily glucose cannot permeate into the cell unless insulin produces some surface change which permits it to do so. The evidence for this hypothesis is in the main of a negative nature, i.e., it rests upon the fact that only with the greatest difficulty or not at all is it possible to demonstrate in vitro effects of insulin and then only in the presence of cellular structure.

The demonstration that insulin does produce changes in the metabolism in cell-free systems would rule out this hypothesis. We have accomplished this demonstration in the case of cell-free extracts of pigeon or rat muscle equilibrated in vitro under suitable conditions. The precise conditions for the constant reproducibility of this effect are not clear, but in two thirds of 80 experiments there was found a significant increase of total oxygen uptake and in about one half of 62 experiments



Exp. no. 69 - Action of Insulin upon, Rat Muscle Extract.

Frg. 16

there was an increase of the respiratory quotient in the presence of added insulin indicating an augmentation of carbohydrate metabolism by the extract. One protocol of the positive results of the series is shown (Fig. 16). On the left the figure shows the oxygen uptake of z cc. of aqueous rat muscle extract without and with insulin at t μ/cc . In the presence of the insulin there was found a marked increase in oxygen uptake in 80 minutes. On the right are shown the respiratory quotients of the samples. With insulin there is an appreciable increase.

In this connection mention must also be made of experiments by Banga, Ochoa and Peters.²² They found with brain dispersion and with pyruvate as a substrate that insulin in vitro not only increased the oxygen consumption but also rendered more complete the oxidation of pyruvic acid.

On the basis of these experiments the exclusion of the physical hypothesis seems reasonable and studies of possible catalytic chemical mechanisms of insulin action appear in order. In the main, discussion has centered about two possibilities: (1) Action upon glycogen synthesis in liver and muscles, and (2) action upon carbohydrate oxidation chiefly in muscles.

Consider first the question of glycogen formation. Experiments with intact animals have told us little about the mechanism of insulin action in this reaction. Indeed, statements are made in the literature that, in the liver, glycogen synthesis is essentially independent of insulin. There are, for example the experiments of Einar Lundsgaard23 who found, following perfusion with fructose enriched blood, just as great a deposition of glycogen in isolated livers from depancreatized cats as from normal cats. Experiments in vitro have, in the main, been equally unilluminating. We have been unable, using liver slices from normal and diabetic cats or normal young rabbits, to influence the glycogen formation by the addition of insulin to the medium. Such has been the experience of others, in particular, Ostern and Holmes²⁴ using normal rabbits. On the other hand, there are reasons for believing that insulin does have an effect upon hepatic glycogen formation. For example, Banting25 found that deparcreatized animals rapidly increase their liver glycogen concentrations following injection of insulin. We have found in depancreatized cats intensively treated with insulin over the relatively short period of 2 to 4 hours increases of hepatic glycogen over initial values. In this connection must be mentioned the experiments of Taubenhaus, Levine and Soskin.²⁶ Using normal rats previously injected with insulin, they found that liver breis equilibrated with glucose showed less glycogen breakdown than did the controls. They concluded that insulin has a direct effect upon hepatic glycogenolysis.

In muscle, glycogen formation appears to be partially independent of insulin action as indicated by experiments of the type presented by Long, Lukens and Fry²⁷ who found glycogen formation from glucose in depancreatized cats although at rate less than normal. But in contrast to the case of the liver, there is ample evidence that insulin markedly accelerates this reaction. It will suffice to mention the recent significant experiments of Gemmill.²⁸ He found using diaphragms from normal rats in vitro, a significantly greater synthesis of glycogen from glucose upon addition of insulin to the medium. This observation has been con-

firmed by Hechter, Levine and Soskin²⁹ and by Stadie and Zapp (unpublished experiments).

But by what chemical mechanism does insulin produce these effects upon glycogen formation in liver or muscle? Hypotheses, of course, must be formulated in terms of the current conception of glycogen formation from glucose. According to the work of Cori, Parnas and others two main steps are involved: (1) A preliminary phosphorylation of glucose to 6-hexose phosphate, and (2) a further transformation of 6hexose phosphate through 1-hexose phosphate to glycogen. The first step of phosphorylation is strictly oxidative and requires the input of energy which must come from the oxidation of specific types of substrates. The efficiency of phosphorylation, i.e., the amount of hexose phosphate and hence potential glycogen formed per mole of substrate oxidized, is known to vary. The recent experiments of Colowick, Kalckar and Cori³⁰ illustrate this. For example, at top efficiency, according to a calculation of Lipmann,31 only one mole of glucose need be sacrificed to bring about the formation of 12 to 24 glycogen equivalents. Since phosphorylation of hexose appears to be brought about by the oxidation of carbohydrate intermediates only, it is possible to propose the hypothesis that insulin, by catalyzing such oxidations, would increase the efficiency of phosphorylation and hence glycogen formation. Such a unitary hypothesis would explain by one common chemical mechanism how insulin promotes carbohydrate oxidation and also regulates glycogen formation. At present there is not direct evidence for it.

The second general step in glycogen formation, i.e., the transformation of 6-hexose phosphate through 1-hexose phosphate to glycogen is non-oxidative and as Cori, Colowick and Cori³² have shown is not influenced by insulin at least when studied in purified enzyme solutions. The effect of insulin in inhibiting formation of 6-hexose phosphate from glycogen reported by Gill and Lehmann³³ is attributed by them to a nonspecific protein reaction with magnesium, a necessary component of the system. Nevertheless, the suggestion has been made by Taubenhaus, Levine and Soskin²⁶ that it is the reversible non-oxidative reaction:

1-hexose phosphate == 6-hexose phosphate

which is influenced by insulin. They propose this hypothesis on the basis of the experiments already quoted in which liver breis from insulin injected normal dogs equilibrated aerobically with added glucose and in-

sulin show diminished formation of free glucose from glycogen.

Apparently these two hypotheses of the chemical action of insulin in glycogen formation or breakdown, namely, on the oxidative phosphorylation of hexose, or on the non-oxidative transformation of hexose phosphate are the only ones seriously considered. At present no decision can be made between them.

ACTION OF INSULIN UPON OXIDATIVE PROCESSES

The problem of the specific chemical action of insulin upon oxidative processes is likewise obscure. I have discussed reasons for believing that insulin plays no direct role in the oxidation of fats. There is little evidence that it affects directly the metabolism of protein although this view has been advocated notably by Bach and Holmes³⁴ who concluded from experiments in vitro with rat liver slices that insulin inhibits the deamination of amino acids in the liver and thereby decreases glyconeogenesis from protein. Our own experiments (Stadie, Lukens and Zapp¹) offer a much different interpretation of this observation, Mirsky^{3t} offers a still different effect of insulin upon protein metabolism, namely, that insulin promotes the synthesis of protein in muscle from amino acids. But if the possible conversion of fat to carbohydrate is ruled out, which appears to be the case, it is difficult if not impossible to integrate the large amount of experimental data on the effect of insulin in the intact normal or diabetic animal except by assuming that insulin has catalytic effects upon the oxidation of carbohydrate.

As representative of the type of experiment which indicates that insulin increases the oxidation by muscle of carbohydrate may be mentioned the work of Cori and Cori. They found in a series of intact rats that insulin doubled the rate of carbohydrate oxidation as compared to controls. These experiments require the calculation of metabolic data from respiratory metabolism. For this reason they have been criticized (Soskin³⁷) but more direct evidence is available. For example, Shorr showed that the isolated muscle from diabetic dogs had a respiratory quotient of 0.7, that of fat, which did not increase upon the addition of glucose or lactic acid, in contrast to the behavior of isolated muscle from normal dogs. Cruickshank showed that the heart from diabetic dogs perfused with glucose containing blood increased its respiratory quotient from 0.7 upward only upon the addition of insulin to the perfusion fluid. Recently we have shown (Stadie, Zapp and Lukens, un-

Fig. 17-Krebs' Citric Acid Oxidative Cycle:

- 1. $\frac{1}{2}$ Glucose (triose) + Fumaric acid + 2 O_2 = Citric acid + CO_2 + H_2O_2
- 2. Citric acid + 1/2 O2 = Alpha ketoglutaric acid + CO2 + H2O
- 3. Alpha ketoglutaric acid + 1/2 O2 = Succinic acid + CO2 + H2O
- 4. Succinic acid $+\frac{1}{2}$ $O_2 = Fumaric$ acid

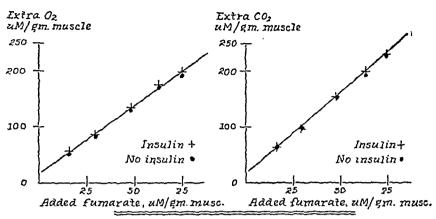
Summation: $\frac{1}{2}$ Glucose + 3 O₂ = 3 CO₂ + 3 H₂O

published experiments), using departreatized cats, that muscle strips taken initially have low respiratory quotients when studied in vitro. Upon subsequent intensive treatment of the cat with insulin over a period of 2 to 4 hours, the isolated muscle increased its respiratory quotient toward 1 indicating a restoration of carbohydrate metabolism.

In spite of this apparent wealth of general evidence, information concerning the specific chemical mechanisms of the catalysis of carbohydrate oxidation by insulin is meager indeed. This is hardly surprising in view of the fact that knowledge of the oxidative processes of carbohydrate metabolism is at present incomplete and confusing. In general, carbohydrate metabolism in muscle involves (1) a glycolytic cycle leading to the formation from glycogen of lactic acid through pyruvic acid, and (2) an oxidative cycle leading to the oxidation to CO₂ and water of the intermediates or end products of the glycolytic cycle.

With respect to the glycolytic cycle the present evidence indicates that it is independent of insulin. On the other hand, with respect to the oxidative cycle there is one which has been proposed by Krebs and Eggleston⁴⁰ in which insulin is supposed to play a role. Briefly the scheme is as follows (Fig. 17).

The C₄ dicarboxylic acids, succinic, fumaric, malic, and oxaloacetic, are present in all tissues and play an important role in intermediary metabolism. According to Krebs, fumaric acid condenses upon oxidation with glucose with the formation of citric acid. Upon further oxidation of the citric acid, alpha ketoglutaric, succinic, and finally fumaric acids are formed thus completing the cycle. Each step is accompanied by oxygen uptake and in the first three there is CO₂ elimination. The final result is the oxidation of glucose to CO₂ and water. Krebs first showed with pigeon muscle in vitro that insulin increased the oxygen uptake in the presence of citric acid or the intermediate C₄ acids. In general, this observation has been abundantly confirmed by Shorr and Barker,⁴¹ by Stare and Baumann⁴² and by Stadie, Zapp and Lukens.² This increase of O₂ uptake has been interpreted by Krebs to mean that insulin, either



Bespiration of depanceatized (2 days) pigeon breast muscle mince in presence of 0.025 M malonate.

F16. 18

by itself or in association with the enzymes of the muscle has catalyzed some step in the cycle.

This discovery of Krebs was indeed significant and aroused hopes that a biological system had been found which would permit the chemical dissection of the insulin effect upon carbohydrate intermediary metabolism. But with further experiment its meaning has become obscure. The citric acid cycle itself has not escaped criticism (see, for example, Stare, Lipton and Goldinger. Further, the effect appears confined to pigeon muscle for Shorr and Barker were unable to find it using muscle from chickens, cats, dogs, or rabbits. Stadie, Zapp and Lukens found the effect independent of the presence of added citrate and they did not find an enhanced effect in the case of depancreatized pigeons. With muscle mince from depancreatized cats they could find no effect whatever.

But whatever its significance the insulin effect with pigeon muscle mince is unquestionably real and we have experimented further with it (unpublished experiments).

In the presence of sodium malonate the reactions of the Krebs cycle are blocked at the succinic acid stage and the individual reactions of the cycle should be more or less isolated. We have been unable by in vitro experiments with pigeon muscle mince to show that any of the individual reactions so isolated are influenced by the presence of insulin in the medium. One illustrative protocol will suffice. The figure (Fig. 18)

| Cat No. | Hypophy- sectomy | Pancrea- tectomy | Experi ment | Cat Weight | Liver Weight | Blood sugar | Liver glycogen | Liver ketone formation per kilo cat per hr. |
|------------|---------------------|---------------------|----------------|---------------|-----------------|--------------------|-------------------|--|
| | 1939 | 1939 | 193 9 | kg. | gm. | my. per cent | per cent | micro- moles |
| 105A | June 8 | June 14 | June 19 | 3.4 | 50 | 60 | 0 04 | 68 |
| 105B | Sept. 7 | Sept. 18 | Sept. 20 | 2.1 | 49 | | 0.02 | 104 |

Fig. 19-Ketone Formation by Liver Slices from Houseay Cat

shows the total oxygen uptake and the CO₂ output in relation to the amount of fumarate added to the medium containing muscle mince. Included in the diagram are observations without and with insulin. There is no difference between the two sets of data. In other words, if, as Krebs states, insulin is a catalyst in any of the intermediate steps of the citric acid cycle the method of isolation of these steps which we have used has failed to localize the insulin action.

Brief mention might be made at this point of another hypothesis which, since its theoretical development by Van Noorden, Falta, and others of the Viennese School, has assumed various guises in the literature. It might loosely be described under the term "hormonal antagonism" or "hormonal balance." The recent classical work of Houssay has re-emphasized it. According to this certain hormones act antagonistically or in a balancing fashion toward each other in respect to the action of each upon the metabolism of the cell. For example, in a depancreatized animal the resultant pituitary excess is perhaps as significant as the lack of insulin. Removal of this excess by hypophysectomy restores the metabolism toward a normal state as in the Houssay animal.

It would be useless in our present state of knowledge to attempt to frame this hypothesis in terms of specific chemical mechanisms. Shorr and his colleagues⁴⁴ in the light of their experiments have framed it in general terms. They found that the metabolism in vitro of cardiac muscle from depancreatized dogs was initially of the diabetic type but upon equilibration for several hours became normal in its ability to oxidize carbohydrate. They suppose a primitive cellular metabolism upon which is superimposed hormonal effects. Because of lack of insulin the cardiac muscle shows an unbalanced type of metabolism which is called diabetic. Within a few hours in vitro, however, unbalancing fac-

tors are removed or destroyed and the metabolism becomes that of the primitive state which in many respects resembles normal.

In this connection experiments from our own laboratory might be cited. We found (Fig. 19) that liver slices from depancreatized-hypophysectomized cats when equilibrated in vitro, in contrast to livers from deparcreatized cats, produced almost no ketones. In fact, the ketone formation was even less than that formed by liver slices from fasted normal cats. The table shows a mean ketone formation of about 90 µM/kg. body weight/hour which is about 1/3 of the value for normal fasted cats and about 8 per cent of the mean value in a series of depancreatized cats. In other respects the hepatic metabolism appeared normal and could be said to be restored to a primitive condition. But the removal of the anterior pituitary has eliminated a factor which enabled the liver to oxidize fats to ketone bodies. Whether this factor is a specific fat oxidation enzyme originating in the pituitary is entirely a matter of conjecture. But the metabolism in this primitive state is less efficient because the ability of the liver to supply a considerable fraction of the total metabolic needs from fat by preliminary partial oxidation to ketones has been lost and the muscles must fall back almost entirely upon the mechanism of direct oxidation to supply their fat calories. A reflection of this inefficiency is perhaps found in the experiments of Lee and Ayres45 who found that hypophysectomized rats as contrasted to normals were relatively limited in their ability to mobilize and use stored body fat and consequently were forced to draw upon body protein to supply energy demands.

The search for the locus of the chemical action of insulin still continues in the laboratories of those devoted to the subject. But one is forced to admit that a survey of twenty years of literature since the discovery of insulin does not reveal conclusive results. The chemical mechanism of insulin action eludes definition and at present there is no unequivocal evidence which enables us to name with certainty any reaction which it mediates, accelerates or inhibits. My feeling is that insulin is a hormonal catalyst, that its action is chemical upon the oxidative processes of the intermediary metabolism of carbohydrates and that eventually its many physiological actions will be explained upon the basis of a single general type of chemical reaction. At all events, the problem of the chemical action of insulin is one of the most interesting unsolved problems in the field of diabetes mellitus.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



DECEMBER 1943

SERUM PROTEINS IN RELATION TO LIVER DISORDERS*

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Introduction

the serum and plasma proteins. It has been shown that they are concerned with the maintenance of tissue equilibrium or homeostasis. The component chiefly contion of the serum has been shown to contain immune bodies. In this fraction also reside factors concerned with blood coagulation. Recent studies by Schoenheimer and others have shown that the serum proteins are substances which are in a dynamic state, constantly being formed and broken down, and that there is a ready exchange between the blood proteins and the body protein stores. 2,3

Evidence is accumulating which suggests that certain of the plasma

^{*} Presented March 4, 1943 at The Stated Meeting of The New York Academy of Medicine Instructor in Medicine, College of Physicians and Surgeons, Columbia University, on leave

| | | | | TABLE I | | | |
|-------|---------|--------|----|----------|------|-------|-----------|
| SERUM | PROTEIN | VALUES | IN | PATIENTS | WITH | ACUTE | HEPATITIS |
| | | | | | | | |

| Serum Albumin grams per cent | 36 Cases at P.B.H.* | 35 Cases in Literature** |
|----------------------------------|------------------------|-----------------------------|
| 2.5 — 3.5 | 6 | 13 |
| 3.6 4.0 | 19 | 11 |
| 4.1 — 5.0 | 11 | 11 |
| Serum Globulin grams per cent | | |
| 1.5 to 3.0 | 25 | 29 |
| 3.1 to 3.5 | 10 | 5 |
| 3.6 to 4.1 | 1 | 1 |

^{*} Data obtained through courtesy of Drs. T. C. Chalmers and F. M. Hanger.

** Data obtained from 5 papers. 5.12

proteins—namely fibrinogen, prothrombin and albumin originate within the liver. It is not surprising, therefore, to find changes in the blood protein constituents when the liver is disordered. The present paper is concerned with a number of these changes seen in liver disease.

ORIGIN OF SERUM PROTEINS

Albumin: Evidence for the liver as the site of origin of serum albumin is largely indirect. Experimental studies, especially those from Whipple's laboratory, have shown that by poisoning the liver of dogs with carbon tetrachloride, the serum albumin level may be reduced. Furthermore, in dogs with Eck fistula or in those poisoned with chloroform or phosphorus, the ability to regenerate serum protein after plasmapheresis is impaired. These findings show that liver damage is associated with a reduced serum albumin level and a reduced capacity of the organism to form serum albumin. In addition, the liver plays an important role as a storage depot for protein. These observations seem to have their clinical counterpart in certain human diseases of the liver, to be discussed later.

Globulin: The evidence for the site of origin of the globulin fraction is less adequate. Sabin⁶ has presented evidence suggesting that globulin may be formed in the reticulo-endothelial cells. She injected rab-

bits with a protein antigen conjugated with dye to make it visible, and she found that it was phagocytosed by reticulo-endothelial cells. After four to seven days, when antibody began to appear, the cells which had taken up the dye appeared to be shedding their surface films into the surrounding fluid. Sabin concluded from these studies that antibody was therefore formed from these cells. Since antibody resides in the globulin fraction of the blood proteins, she suggested that the reticulo-endothelial cells might be the site of origin for normal serum globulins. It is noteworthy that states of hyperglobulinemia are frequently associated with diseases in which there is a marked involvement of the reticulo-endothelial tissue, such as leukemia and multiple myeloma.

Fibrinogen and Prothrombin: There is much experimental evidence indicating that both these protein constituents are formed in the liver. Liver damage induced by hepatotoxin and by hepatectomy is associated with decreased plasma prothrombin and fibrinogen.⁷

CHANGES IN SERUM PROTEINS IN LIVER DISEASE

Acute Liver Disease: In acute hepatitis ("catarrhal" jaundice; arsphenamine poisoning; cinchophen poisoning) there generally is only moderate alteration in the serum proteins, as determined by salt precipitation methods. Table I shows the values for serum albumin and serum globulin in thirty-six patients with acute hepatitis on admission to the Presbyterian Hospital, and in thirty-five cases collected from the medical literature.8-12 In most instances these determinations were made within two weeks of the onset of jaundice. If 4 grams per cent of serum albumin be considered the lower limit of normal, roughly twothirds of the series showed decreased albumin, but the degree of reduction was slight. Likewise if a value of 3.0 grams per cent of serum globulin be taken as the upper limit of normal, roughly one-fourth the series showed slight increase of this fraction. When the disease process is more protracted or severe, as in acute or subacute yellow atrophy, these changes in serum proteins may become very pronounced. Finally, in the stage of chronic hepatitis or cirrhosis of the liver, the serum albumin characteristically is reduced. These findings may indicate that in acute hepatitis the body and liver stores for serum albumin are sufficient to tide over the emergency of a short lived disease. Since the tissue depots are drained first, a decrease in the serum albumin might not appear until the stores were depleted.

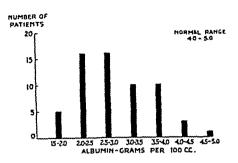
Although values for serum globulin may be only slightly altered in acute hepatitis, as seen in Table I, there is generally a qualitative change in the globulin component, which is considered to be more or less distinctive for liver damage. This qualitative change apparently resides in the euglobulin fraction, ^{13, 14, 15} and it is reflected by such tests as the cephalin flocculation reaction, Takata-Ara reaction and colloidal gold test. ¹⁶

Significant changes of plasma fibrinogen seldom are seen in either acute or chronic hepatitis unless the disease process is advanced, as in acute yellow atrophy. This implies that the reserves for this clotting factor are far in excess of normal demands.

Studies with experimental animals have shown that the prothrombin level is decreased more rapidly than fibrinogen following hepatectomy or chloroform poisoning. Clinical observations bear this out, since changes in prothrombin occur rapidly after the onset of acute hepatitis. This suggests either that the body stores are less ample, or that prothrombin is a more labile substance which is readily exhausted or destroyed by liver damage. Moreover the administration of vitamin K fails to restore a normal value for prothrombin in the presence of severe liver damage. This failure of the organism to respond to vitamin K has been used as a test for impaired liver function. Since much has been written on this subject, we should prefer not to dwell on it further at this time, but rather to discuss changes of the serum proteins in chronic liver disease, with which we have had more experience.

Chronic Liver Disease: The serum proteins are consistently altered in cirrhosis of the liver. The original observation of Filinski, showing a decrease of serum albumin and increase of serum globulin in the presence of cirrhosis of the liver, has been confirmed from many sources. During the course of a study of this disease, begun in 1936, repeated observations were made on the serum proteins in many patients. Some of the results of this study have been recorded elsewhere. Figure 1 shows the frequency distribution of the serum albumin and globulin levels of sixty-one patients with cirrhosis of the liver on entry to the hospital. These patients exhibited various stages of the disease process. Some had ascites with jaundice, whereas others had only ascites or jaundice. In still others the presenting problem was hematemesis. The data in this chart confirm the reported tendency toward reduction of serum albumin and elevation of serum globulin in this disease.

SERUM PROTEIN VALUES IN GI CASES



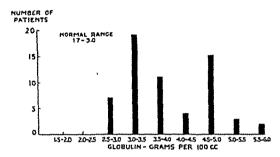


Fig. 1—Frequency distribution of serum proteins in 61 cases of cirrhosis of the liver. The serum albumin tends to be reduced and the serum globulin to be increased.

Relation of Serum Proteins to the Clinical Course of Laennec's Cirrhosis: A number of authors^{8, 9, 10, 11, 24} have suggested that there may be a correlation between the severity of liver disease and alterations in the serum albumin and globulin. We have analyzed our data with respect to this problem. Of twenty patients who died after an average hospital stay of three months, the mean level of the serum albumin was 2.4 grams per cent on entry to the hospital. Of twenty-eight patients who improved, as measured by disappearance of ascites and gain in weight and strength, the mean value for the serum albumin was 3.0 grams per cent, on admission. The difference between these two levels is statistically significant. Figure 2 shows the frequency distribution of the albumin values of these two groups of patients.

All of the twenty patients who died had ascites, and but two showed a temporary improvement. Their admission serum albumin levels were 2.9 and 3.3 grams per cent, respectively. Of these twenty patients who died, 70 per cent had albumin levels below 2.5 grams per cent on admission. Of the twenty-two patients who had ascites on admission, but

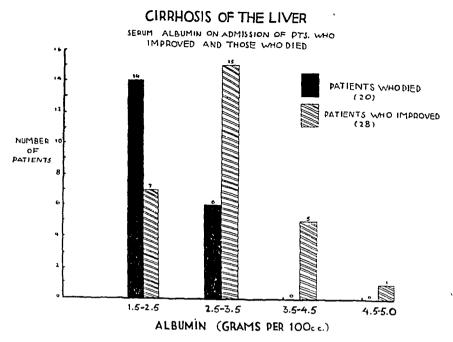


Fig. 2—Frequency distribution of serum albumin in relation to prognosis as to duration of life. This chart shows the values on admission to the hospital. The initial serum albumin values were lower for patients who subsequently died than for those who improved.

who improved subsequently, 70 per cent had albumin levels greater than 2.5 grams per cent. Thus it appears that the prognosis as to duration of life becomes increasingly grave as the serum albumin level decreases.

Examination of the values for the serum globulin and serum total proteins fails to reveal any significant differences between the patients who improved and those who died.

Wiener and Wiener^s cited three cases in which changes of the serum proteins correlated fairly well with the clinical course of the patients. Foley, Keeton, Kendrick and Darling¹¹ reported data on one patient with cirrhosis of the liver and ascites, whose ascites disappeared and whose clinical improvement was associated with a return of serum protein values to normal during a period of seven months. Conn, Newburgh, Johnson and Sheldon²⁵ recorded data on the serum proteins of one patient with chronic liver disease, in whom improvement was associated with a rise in serum albumin to normal. The patient had no ascites. Except for these few instances there has been little recorded evidence indicating that changes in serum proteins may reflect changes in the disease process. We have examined the serum protein levels of

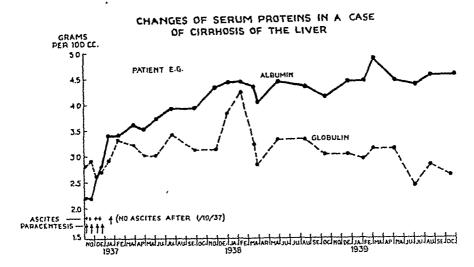


Fig. 3-Serum proteins in a patient who showed clinical improvement.

our patients in order to determine whether there is any correlation between the blood protein fluctuations and the clinical course.

Figure 3 shows the value of serum albumin and globulin in a patient who improved and remained in good general health for more than three years. On admission the serum albumin was very low, and the globulin was elevated. Repeated paracenteses had been performed for several months prior to hospitalization and during the first portion of the hospital stay. With clinical improvement there was a sustained rise of serum albumin to normal values. The globulin tended to fall. From 1939 to 1942 she has been well except for one period of decompensation with ascites, which was associated with a decrease in serum albumin. She recovered from this, and she has been well for the past one and one-half years. This pattern of response has been seen repeatedly in patients who have improved and remained in good health.

In contrast to the above findings, Figure 4 illustrates changes of serum proteins in a patient whose course was that of clinical failure. This patient, who was very ill at entry, required frequent paracenteses. After nine months in the hospital the patient died. The progressive decline of serum albumin is typical of this group. However, the decline of serum globulin observed in this patient is not usually encountered.

There is a third group of patients which seems to conform to a third pattern. Figure 5 charts the serum proteins of such a patient. On admission this man had massive ascites, edema and jaundice. Repeated

CHANGES OF SERUM PROTEINS IN A CASE OF CIRRHOSIS OF THE LIVER

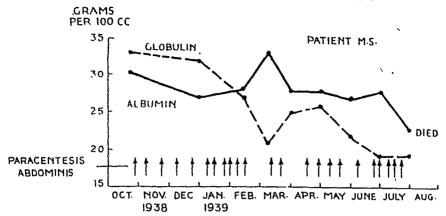


Fig. 4—Serum proteins in a patient with clinical failure.

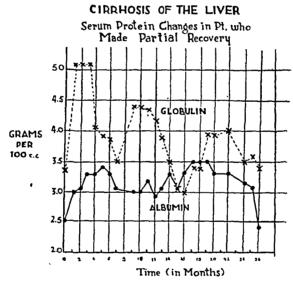


Fig. 5-Serum proteins in a patient who showed partial improvement.

paracenteses had been performed in the past. During the first six weeks of hospitalization there was marked clinical improvement with loss of ascites, and subsequent weight gain of 20 pounds. For the next two years he remained in fairly good health but the serum albumin, after an initial rise, did not return to normal. After about two years of hospitalization he was permitted to leave. He returned after three weeks with massive edema and ascites, and he died within three days. There was a sharp decrease in serum albumin before death. The diagnosis of cirrhosis of the liver was confirmed at necropsy. This pattern of blood

proteins has been seen in other patients who lost ascites and improved clinically for long periods of time, but whose course was ultimately unfavorable.

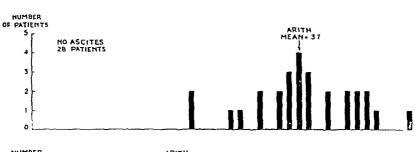
From these data it appears that the changes in level of the serum albumin have a good correlation with the clinical course. In those patients who improve and remain in good health for indefinite periods of time, the serum albumin rises to normal values and remains within that range. In those patients who show only temporary improvement, the serum albumin increases but does not reach normal levels. Here the prognosis is guarded despite temporary states of apparent well-being. In those patients whose course is unfavorable, the serum albumin either remains low or declines.

RELATION OF SERUM PROTEIN LEVEL TO FORMATION OF ASCITES

Following Starling's²⁶ work on the role of the serum proteins in the maintenance of the colloid osmotic pressure of the blood, numerous investigators have stressed the important relationship between alterations in the blood protein level, particularly the albumin level, and the transudation of edema fluid. In the edema of nephrosis,^{27,28} nephrotic stage of glomerulonephritis²⁹ and in protein starvation,³⁰ this correlation has been shown. With regard to ascitic fluid in cirrhosis of the liver, Loeb, Atchley and Palmer³¹ have shown that it has the properties of a transudate. Many workers have presented data to show a correlation between the reduced level of the serum albumin and the accumulation of ascites.^{9,32,33}

Our data are in accord with these reports. Figure 6 shows the frequency distribution of serum albumin levels in forty-three patients with ascites and in twenty-eight patients without ascites. The values for the forty-three patients with ascites were obtained on admission to the hospital. Values for serum albumin in patients without ascites were derived from two sources. In thirteen cases the data are admission values, whereas in fifteen cases the data are values in patients who lost ascites during their hospital stay. Values for the latter group were taken two months after diuresis was considered complete. The mean serum albumin level for the patients with ascites was 2.3±0.1 grams per cent, whereas that for the patients without ascites was 3.7±0.8 grams per cent. The difference between these values is statistically significant. The values for serum globulin and serum total protein are not signifi-

SERUM ALBUMIN IN PATIENTS WITH AND WITHOUT ASCITES



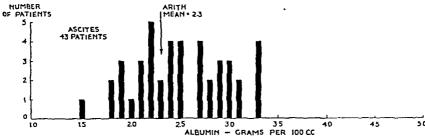


Fig. 6—Frequency distribution of serum albumin in patients with and without ascites. The serum albumin is significantly lower in the group with ascites. (B)

cantly different. Thus the accumulation of ascites may be correlated with the level of the serum albumin. There is another important factor in the formation of ascites, namely, portal hypertension. Thompson, Caughey, Whipple and Rousselot34 have demonstrated splenic vein hypertension in Banti's syndrome. Bellis35 has demonstrated portal hypertension in one patient with cirrhosis of the liver and ascites, and Mc-Indoe36 has shown increased resistance in the cirrhotic liver to perfusion via the portal vein. It seems likely that reduced serum albumin is an essential factor in the transudation of the fluid, whereas portal hypertension determines the site at which the transfer of fluid takes place. The serum globulin does not seem to play a critical role. These data have been helpful in evaluating the course of ascites in particular patients. We have observed that when ascites occurs in the presence of normal serum albumin, one should suspect an extrahepatic cause, such as portal vein thrombosis or carcinoma involving the porta hepatis, as a contributory factor to the accumulation of ascites.

RELATION OF THE SERUM PROTEIN LEVEL TO DIURESIS

In 19 instances of diuresis in 17 patients, the mean serum albumin level at which this phenomenon occurred was 3.1 grams per cent and

the mean serum globulin level was 4.1 grams per cent. It is difficult to establish the time at which the onset of diuresis takes place because this phenomenon may persist for weeks. However, the serum albumin level of 3.1 is near the transition point between the two groups of patients noted in Figure 6. It is noteworthy that the level of 3.1 grams is higher than the commonly accepted critical level for edema of 2.5 grams in hypoproteinemia from other causes. This may be due to the added factor of portal hypertension. It is seen that the serum albumin rises in patients who improve and lose their ascites. This may not necessarily represent a "cause and effect" relationship, since both phenomena might reflect improved liver function.

NITROGEN BALANCE IN CIRRHOSIS OF THE LIVER

Data have been presented which show that the liver plays an important part in the formation of serum albumin. From the afore-mentioned clinical studies, it appears that the level of the serum albumin may be correlated with the clinical course of circhosis of the liver, as well as the appearance and disappearance of ascites. We are next concerned with the cause of this protein abnormality in liver disease.

Some authors³⁷ have ascribed the decreased serum albumin of cirrhosis of the liver to insufficient protein intake, whereas others^{9, 11} have suggested impaired protein synthesis as the mechanism. It is obvious that hypoalbuminemia could be caused by protein starvation, by excessive utilization, or by impaired synthesis.

Patients with starvation hypoalbuminemia differ from those with low serum albumin in liver cirrhosis in that elevated serum globulin seen so commonly in cirrhosis, does not occur. The reduction in serum protein is at the expense of the albumin alone in starvation. In cirrhosis of the liver the total protein is usually normal. A second point of difference is that the low serum albumin of starvation generally responds within ten to twenty days with a rise in serum albumin, if one or two grams of protein be fed per kilogram of body weight per day. Although the antecedent diets of patients with cirrhosis of the liver are deficient in protein sources, such as meat and dairy products, these individuals do not show such prompt improvement in serum albumin after high protein feeding. Furthermore, the experimental studies reviewed by Madden and Whipple show that the low serum albumin levels in dogs, maintained on a low protein diet and plasmapheresis, may be



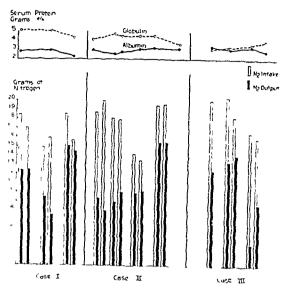


Fig. 7—Nitrogen balance studies in 3 patients with cirrhosis of the liver. Although all patients were in positive nitrogen balance there were no changes in serum proteins.

rapidly restored to normal after adequate protein feeding. When dogs are kept on low protein intake for twenty-one days rapid restoration of serum albumin to normal occurs. However when the period of low protein feeding is maintained for long intervals, eighty-five days or more, regeneration of serum protein levels to normal is impaired.³⁹ After prolonged periods of low protein feeding, histological³⁰ and functional changes⁴⁰ are said to occur in the liver. These changes may be part of a pattern of impaired liver function with associated faulty albumin synthesis.

In order to determine the nature of the hypoalbuminemia of cirrhosis of the liver, nitrogen balance studies were performed in 5 patients with low serum albumin and ascites. Grabfield and Prestcott⁴¹ have reported positive balance in one patient with cirrhosis who had normal serum proteins. Although balance studies were not performed, Myers and Keefer⁹ showed that high protein feeding over a limited period of time did not produce changes of serum albumin in 4 patients with decompensated Laennec's cirrhosis. In the present balance study, patients were fed a standard diet (containing C 280, F 100, P 100) for 4 to 6 weeks before the study was begun. In three subjects the nitrogen bal-

NITROGEN BALANCE IN A PATIENT WITH CIRRHOSIS OF THE LIVER

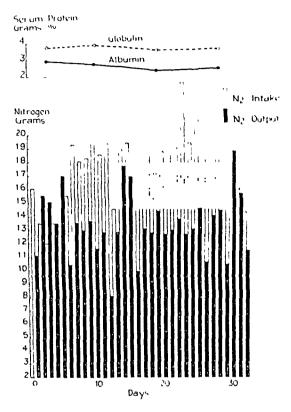


Fig. 8—Nitrogen balance in one patient with cirrhosis of the liver studied for 32 days. The findings are similar to those in Figure 7.

ance was determined for forty-eight hour periods at two week intervals. Figure 7 shows the results in this group. In two subjects the daily balance was determined for twenty-five and thirty-two days respectively. Figure 8 represents the findings in the latter study. In all instances the patients were in positive balance. They were retaining nitrogen. In addition, normal values for fecal nitrogen showed that gastrointestinal absorption was normal. In no instance was there a sustained and striking rise in the serum albumin. The non-protein nitrogen and serum globulin levels did not reflect this retention of nitrogen. For example, one patient (Figure 8) retained 849 grams of protein as nitrogen, without a significant increase in the blood protein or non-protein nitrogen constituents.

This type of balance pattern differs clearly from that found in

nutritional hypoproteinemia.^{38, 42} Whipple¹³ has shown that there normally exists a ready exchange between the body protein stores and the blood proteins, and that the latter are reduced only after the body protein stores have been depleted. When protein is made available there is a rapid rise in blood protein level. It appears from the data presented, that in the patients with cirrhosis of the liver and hypoalbuminemia, the restoration of the serum albumin to normal is impaired. It is likely that the retained nitrogen is being converted to body protein and not to blood protein (albumin), a change from the normal which suggests faulty synthesis of serum albumin.

SUMMARY AND CONCLUSIONS

Evidence has been reviewed which indicates the liver as the probable site of formation for blood albumin, fibrinogen and prothrombin. Data have been presented to show the effects of liver disease, acute and chronic, on the protein constituents of the blood.

In acute liver disease the fibrinogen and prothrombin levels may be reduced. The albumin may show slight reduction and the globulin moderate elevation. In more severe forms of acute liver disease these changes may be pronounced.

In chronic liver disease, notably cirrhosis of the liver, the serum albumin generally is reduced, whereas the serum gobulin is normal or increased. The degree of reduction in the albumin level seems to be correlated with the prognosis as to duration of life, clinical course of the disease, and with the appearance and disappearance of ascites.

Nitrogen balance studies in cirrhosis of the liver show that patients with this disease can absorb and retain protein, but that there is an apparent defect in synthesis of serum albumin.

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DIAGNOSTIC SIGNIFICANCE OF SERUM ALKALINE AND ACID PHOSPHATASE VALUES IN RELATION TO BONE DISEASE*

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Phosphatase, like enzymes in general, is known by its activity. This activity is manifested in: (1) the liberation of inorganic phosphate through hydrolysis of organic phosphorus compounds; and (2) under changed conditions, the utilization of inorganic phosphate in the synthesis of organic phosphorus compounds. As our title implies, there is more than one phosphatase, and indeed there are many. The pH at which the optimum activity of a phosphatase takes place furnishes a basis for the broad classification of phosphatases as so-called alkaline and so-called acid phosphatase 5. The former acts optimally at a distinctly alkaline pH (for instance, pH 9) and the latter at a distinctly acid pH (for instance, pH 5).

The alkaline phosphatase is by far the more widely distributed in the tissues of man. It is found in relatively high concentrations in the intestinal mucosa, kidneys, liver, ossifying cartilage, bone, and leukocytes. It is also normally present, but in relatively smaller amounts, in the blood serum. In regard to the functions of alkaline phosphatase in vivo, there is some evidence that it plays a role in the absorption of glucose through the intestinal wall, the reabsorption of glucose in the renal tubules, and the formation of osseous tissue.

The acid phosphatase is found in particularly high concentrations in the prostate after puberty. It occurs especially in the acinar epithelium of that gland; is apparently elaborated by this epithelium; and is excreted as a constituent of the prostatic fluid. The spleen and brain, too, contain a good deal of this phosphatase, though by no means as much

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as the prostate. It is present in other tissues, also, including the red blood cells, at least in small amounts. The serum shows extremely little acid phosphatase activity—in fact, much less even than alkaline phosphatase activity. As to the function of acid phosphatase, much further elucidation is needed. In vivo as well as in vitro it seems to play a role in glycolysis through its action on hexose phosphates. In the prostatic ejaculate of man it may, by this means, help to provide the energy required by spermatozoa for survival and motility.¹

Before proceeding, it may be well to point out that the alkaline phosphatase and acid phosphatase categories apparently comprise a number of phosphatases which are not identical. However, the secondary differences between, for instance, the alkaline phosphatase of the intestine and that of the kidney, or between the acid phosphatase of the prostate and that of the spleen, need not occupy us here.

What we are concerned with is exclusively the alkaline phosphatase

What we are concerned with is exclusively the alkaline phosphatase and acid phosphatase activity of the serum, and the significance of aberrations of their values in relation to disease, especially of the skeleton. Under conditions of disease, the alkaline phosphatase activity level of the serum may fall below or rise above the normal level. Elevations of this level are more significant and more common than drops, and are associated particularly with skeletal disorders and disorders of the liver and biliary passages. The acid phosphatase activity is significant diagnostically in that it nearly always rises above the normal level in cases of carcinoma of the prostate which has metastasized. Indeed, a high acid phosphatase activity value has come to be regarded as an important indication of the presence of this disease.

ESTIMATION OF SERUM ALKALINE AND ACID PHOSPHATASE ACTIVITY

The methods for the determination of alkaline phosphatase activity of serum (or plasma) were developed first. The method of Kay,² published in 1930 and used in some of the earliest clinical investigations of serum phosphatase activity, was soon found impractical, even by Kay himself. It was replaced in 1932 by that of Jenner and Kay,³ but the latter method seems likewise to have been largely abandoned. On the other hand, the method of Bodansky,⁴ first briefly reported in 1931 and fully described in 1933, came to be widely employed and apparently still is. The only other method which seems to be extensively used for the determination of the alkaline phosphatase of the serum is that of

King and Armstrong,⁵ published in 1934. Both the Bodansky method and the King and Armstrong method have since been adapted to the determination of serum acid phosphatase activity also.

The principle underlying the Bodansky method of determining alkaline phosphatase activity is the estimation of the amount of phosphorus liberated as phosphate ions by a given amount of serum, incubated with a substrate containing sodium beta-glycerophosphate buffered to a constant alkaline pH of 8.6 by sodium diethylbarbiturate. The phosphatase activity value of any particular serum specimen is expressed in units. Specifically, this value, as determined by this method, represents the calculated number of mg. of phosphorus which 100 cc. of the serum can liberate in one hour as phosphate ions from the buffered substrate under the conditions of the test.

The principle underlying the King and Armstrong method of determining alkaline phosphatase activity is the estimation of the amount of phenol liberated by a given amount of serum incubated with a substrate containing disodium phenyl phosphate buffered to an alkaline pH of 9.0, again by sodium diethylbarbiturate. The units of phosphatase activity of any particular serum represent the calculated number of mg. of phenol which would be liberated by 100 cc. of the serum in one-half hour under the conditions of this test method.

As noted, both the Bodansky and the King-Armstrong methods for the determination of serum alkaline phosphatase activity can be adapted to the determination of serum acid phosphatase activity. The adjustment depends essentially upon the use of a substrate-buffer combination which (at least theoretically) will completely inhibit the activity of the alkaline phosphatase of the serum and at the same time permit optimal activity of the small amount of acid phosphatase which is also present.

Gutman and Gutman⁶ adapted the method of King and Armstrong to the measurement of acid phosphatase activity by using a mixture of citric acid and sodium hydroxide as the buffer for the sodium phenyl phosphate substrate (to bring the pH to 4.9) and incubating for one hour. In our laboratory, the Bodansky method for determining serum alkaline phosphatase activity is adapted to the determination of serum acid phosphatase activity by adding acetic acid to the sodium beta-glycerophosphate-diethylbarbiturate substrate (so as to bring its pH to 5.0) and incubating for three hours.⁷ The acid phosphatase activity value of the serum equals the calculated number of mg. of phenol or

phosphorus, respectively, which 100 cc. of the serum can liberate in one hour from the buffered substrate under the standard conditions of the tests.

RANGE OF VALUES FOR SERUM ALKALINE PHOSPHATASE

For alkaline phosphatase as determined by the Bodansky method, most values for adults range between 2.0 and 3.5 units per 100 cc. of serum and average about 2.8 units. In fact, they lie so strictly within this range that any value even very slightly above 4 units may be suspected of being abnormal. For children, the normal values lie between 5 and 14 units and average about 7.5 units. Values of 10 to 14 units are more likely to be found in children between the ages of ten and fifteen than in those up to ten years of age. In children, values near the upper limit of the normal range should arouse attention, and values of 18 units or more are to be considered clearly abnormal. For infants a few months of age, the normal values lie between 10 and 20 units and values between 20 and 25 are not yet necessarily abnormal, though they deserve special attention.

For alkaline phosphatase, as determined by the method of King and Armstrong, most values for adults lie between 5 and 10 units per 100 cc. of serum and average about 8 units. Values below 3 and above 13 begin to fall within the range of the abnormal. King and Armstrong themselves give but few data on the values for children, but reports by others using their method indicate values of 15 to 25 for children, with an average of about 20.

SERUM ALKALINE PHOSPHATASE VALUES IN RELATION TO DISEASE*

As noted, under conditions of disease in the body, the serum alkaline phosphatase value may either fall below or rise above the normal level. Values below 2.0 Bodansky units are observed occasionally in "normal" adults. More regularly they are found in adults suffering from surgical hypoparathyroidism. Cachectic adults, also, very often show abnormally low values, even if the cachexia has developed on the basis of malignancy, provided the latter is not metastatic to the liver or skeleton.

^{*} These values will be stated throughout in terms of Bodansky units only. Within the normal range the Bodansky values are roughly about ½ as great as the King-Armstrong values. However, in the abnormal range, this proportionality no longer holds, the Bodansky values rising very much more steeply. Thus, one cannot, in the high upper range, convert a Bodansky value into a King-Armstrong value or vice versa by multiplying or dividing, respectively, by 3. Control study of the question of high abnormal values by the use of mixed sera leaves no doubt in our mind of the accuracy of the high values as determined by our method.

On the other hand, a pronounced leukocytosis tends to increase the value slightly, often not even beyond the upper limit of the normal (4.0 units).

We pass on now to consideration of the numerous disorders of the skeleton in which elevation of serum alkaline phosphatase values may have considerable diagnostic significance. Our experience in this connection runs back over more than 10 years and followed closely in the wake of the studies by Kay⁸ and Roberts. Between 1931 and 1939, we published a number of articles, to both clinical and experimental, containing abundant data on elevations of the serum alkaline phosphatase value in relation to skeletal (and also hepatic) disorders. These findings have been corroborated by others and continue to be confirmed by our current experience, based on a large volume of additional clinical and experimental material. Here, therefore, we are limiting ourselves, in the main, to summaries of, and conclusions from, this experience.

Before proceeding, however, we wish to point out that an abnormally high serum alkaline phosphatase value, though it does have diagnostic significance, frequently has to be considered in conjunction with other blood chemistry data in arriving at a definite diagnosis. It is true that even by itself a spectacularly high serum alkaline phosphatase value in an adult (100 to 150 units) almost surely indicates the presence of Paget's disease, and in a young child (75 to 100 units) rickets. On the other hand, an abnormally but not spectacularly high serum alkaline phosphatase value must often be considered in the light of the serum calcium, inorganic phosphate, NPN, and total protein values when one is attempting definitive diagnosis of a skeletal abnormality.¹²

In evaluating elevations of the serum alkaline phosphatase in the differential diagnosis of bone disease it must always be borne in mind that high alkaline phosphatase values are found also in connection with various disorders of the liver, including those of the biliary passages. Therefore, before drawing conclusions on the relation of a high phosphatase value to skeletal involvement in a given case, it is necessary to consider the possibility of involvement of the liver. We do not wish, however, to enter into the particularly complex question of the significance of elevated serum alkaline phosphatase values in relation to the differential diagnosis of liver disease with or without jaundice. We wish merely to point out that it is important in connection with hepatic dis-

orders, just as in skeletal disorders, to interpret the elevated alkaline phosphatase value in the light of other findings. Specifically, in connection with hepatic disease, the elevated alkaline phosphatase value must be considered in the light of the serum cholesterol value, cholesterol ester (or free cholesterol) per cent, bilirubin value, protein fraction values, and cephalin flocculation test result.

Paget's Disease: To date, we have accumulated findings on about 70 cases of this disease. In fully half of these the disease was of limited extent (that is, involved at most only a few bones). The cases presenting limited involvement yielded alkaline phosphatase values ranging between 5 and about 25 units and distributing themselves rather evenly along this range. On the other hand, in the cases presenting widespread skeletal involvement, the values, with few exceptions, ranged between 50 and 125 units. One exception was a case in which it was only 15 units, and this was the only case in which it was below 50 when the skeletal involvement was extensive. The explanation for the low value in this case may be that the disease had gone on to healing, as was revealed by histologic examination of many bones removed at autopsy. The highest value observed among our patients with widespread Paget's disease was 258 units. The dramatically high value in this case may be related to the fact that many of the involved bones were the site of osteogenic sarcoma.

Altogether, one can take the alkaline phosphatase activity value as a rough index of the severity of the disease process, and cases of Paget's disease showing values of about 75 to 150 units are certainly very active clinically. It is also of interest that ordinarily, so far as any particular case is concerned, the phosphatase value does not tend to vary much, at least over an interval of a year or so. Indeed, we have observed only one case which violated this rule. In that case, the phosphatase value doubled in the course of 16 months, rising from 70 to 142 units. Subsequently, this patient died of sarcoma complicating the Paget's disease.

Finally, it should be noted that in Paget's disease the serum calcium and phosphorus values are ordinarily normal. However, it has been found that an occasional case of Paget's disease is complicated by, or at least concomitant with, hyperparathyroidism. In these cases, a definite hypercalcemia is of course present, but the fact that removal of the offending parathyroid tissue has no influence upon the course of the Paget's disease indicates the independence of the two disorders.

Rickets of Infancy and Early Childhood: This is another disease in which the serum alkaline phosphatase value may be found very high. To date we have accumulated pertinent findings on about 100 cases. Some of the affected infants and young children had had no antirachitic therapy, while some had had inadequate therapy; some were admitted with full-blown rickets and even tetany, and others with substantially healed rickets and residual deformities. In short, these cases represent the variety of rachitic material which usually accumulates in hospital practice. Accordingly, our cases presented a wide range of serum alkaline phosphatase values.

On the basis of the phosphatase values on the one hand and the severity of the rickets (as revealed by the clinical and roentgenographic findings) on the other, the cases fell into certain groups. On admission in the clinically mild cases the values were roughly 20 to 30 units, in the moderately severe cases up to 60 units, and in the very severe cases above 60 units and up to 190 units. Thus there was, on the whole, a definitely positive correlation between the severity of the clinical condition on the one hand and the degree of alkaline phosphatase activity of the serum on the other. In harmony with this correlation, many of the cases admitted merely for correction of rachitic deformities yielded normal phosphatase values, and clinical and roentgenographic examination showed that the rickets was healed, irrespective of the immediate external impression which these cases may have created.

It is interesting also to examine the serum calcium and inorganic phosphate values on admission in relation to the corresponding phosphatase values. The serum calcium value was not ascertained in all cases, but of those in which it was, about one-third showed a definite hypocalcemia (less than 9 mg.), one-third a suggestion of hypocalcemia (9 to 10 mg.), and one-third no hypocalcemia (10 to 10.7 mg.). However, there was no reliable correlation between serum calcium and the severity of the rickets in the different cases on admission. On the other hand, the serum inorganic phosphate value, while known to be a much more reliable index of the severity of rickets than the serum calcium, was still not as uniformly reliable as the serum phosphatase value. Though a distinct depression of the inorganic phosphate level to 3 mg. or less was associated in general with the higher phosphatase values (at least 50 or 60 units), some high phosphatase values were found also with inorganic phosphate values between 3 and 4 mg. or even higher.

Altogether, the alkaline phosphatase value is not only a good index of the severity of the rickets but usually also a better guide to the adequacy of the antirachitic treatment and a more accurate indication of the complete abolition of the rachitic state than the calcium value or even the phosphorus value. Specifically, the inorganic phosphate is likely to rise promptly even under somewhat inadequate treatment. The phosphatase value drops decidedly only when the antirachitic treatment is adequate, and does not reach the normal level in its fall until the healing of the rickets is really complete.

Hyperparathyroidism: În 15 cases of so-called primary hyperparathyroidism we obtained initial alkaline phosphatase values ranging from 4.5 to 35 units—that is, from just above the upper limit of the normal to over twelve times the normal average. In these cases, there was a rough positive relation between the level of the phosphatase value and the severity of the skeletal alterations as ascertained roentgenographically. Indeed, in two cases in which the initial values were 4.5 and 4.6 respectively, osseous changes were so inconspicuous that they could easily be overlooked roentgenographically. The first of these two cases was followed for 15 months before the offending parathyroid tissue was removed. During this time, the phosphatase value rose from 4.5 to 7.6 units, and concomitantly one could observe some increase in the bone changes detectable roentgenographically.

After removal of the offending parathyroid tissue in a case of hyper-parathyroidism, the less elevated the pre-operative phosphatase value has been (and accordingly the less pronounced the skeletal alterations) the more rapidly does the value drop to the normal level. Thus, in the case just mentioned, in which the phosphatase value had risen only to 7.6, only five months elapsed before it was down to the normal level of 2.7. On the other hand, in a case in which the pre-operative phosphatase value was 23 units (and in which incidentally the bone changes were very severe) it was only in the course of 3 years that the phosphatase value finally came down to the distinctly normal level of 2.2 units. The return of the phosphatase value to a normal level signifies that recalcification of the skeleton has been completed.

In cases of secondary (renal) hyperparathyroidism the serum alkaline phosphatase values parallel those seen in primary hyperparathyroidism, in accordance with the severity of the bone changes. In one of several cases which we studied, the initial phosphatase value was 23

units. Accordingly, in this case, the patient, an adult, showed osseous changes which were quite pronounced roentgenographically. It may also be worth noting in this connection that they were indistinguishable from changes to be observed roentgenographically in a correspondingly severe case of primary hyperparathyroidism. Indeed, anatomically too, the osseous changes of primary and secondary hyperparathyroidism in adults are indistinguishable.

Osteomalacia: In three instances of a rare type of non-puerperal bone-softening in adults, which represents this country's closest approximation to genuine osteomalacia, the serum alkaline phosphatase values were 10.3, 11.1, and 13.5 units respectively. In these cases, the serum calcium and inorganic phosphate values were low, as they are in genuine osteomalacia. One of these cases came to autopsy, and the bone changes found could not be differentiated anatomically from those of genuine osteomalacia. Nevertheless, this case, like the other two cases, is puzzling in that it was refractory to the usual treatment for osteomalacia (that is, a high calcium diet and a high vitamin D intake).

Non-Tropical Sprue: In three instances of non-tropical sprue in adults, the serum alkaline phosphatase values were 5.6, 8.2, and 10.8 units respectively. Furthermore, these cases all presented pronounced hypocalcemia and mild hypophosphatemia. In all 3 instances, the bones were more or less porotic.

One must point out, however, that in cases of menopausal osteoporosis much more pronounced and indeed devastatingly severe osteoporosis may occur and yet the phosphatase, calcium, and inorganic phosphate levels all remain within normal limits. Perhaps the osteoporosis in these cases represents an exaggerated manifestation, in the skeleton, of the post-menopausal involutional processes going on in the body as a whole. Indeed, in merely senile osteoporosis the phosphatase, calcium, and inorganic phosphate values of the serum are usually also not abnormal, although again the bone thinning may be very pronounced.

Osteogenic Sarcoma: At first admission for treatment, a case of osteogenic sarcoma may or may not show an elevation of the alkaline phosphatase value. Of the eleven cases tabulated in Table 1, there are four in which the value could legitimately be regarded as definitely above normal for the age of the patient. In two, it might be regarded as just above the normal (age 18–4.3 units; age 26–4.1 units). Furthermore, it appears to us from the data in this table (though the series is small)

| TABLE I |
|-----------------------|
| OSTEOGENIC SARCOMA |
| (Values on Admission) |

| Age | Alk # E | Site | Follow Up | Age | Alk # E | Site | Follow Up | |
|-----|------------|------|--------------|---------------------------------|------------|------|--------------|--|
| 10 | 7.7 | F. | Died 16 mo. | 26 | 4.1 | Н. | Alive 10 mo. | |
| 13 | 42.4 | F, | Died 6 mo. | 32 | 3.0 | Н. | Died 6 mo. | |
| 15 | 6.1 | F. | None | 42 | 16.6 | F.* | None | |
| 16 | 4.1 | F. | Alive 1 yr. | 44 | 2.7 | F.† | Died 4 mo. | |
| 18 | 4.3 | I. | None | 53 | 228 | F. | Died 8 mo. | |
| 21 | 9.3 | F. | Died 2 yr. | F.—Femur; H.—Humerus; I.—Ilium. | | | | |

^{*} Pulmonary metastases.

E == Phosphatase

that the initial phosphatase value offers no indication of the relative rapidity with which death will ensue. (In our experience, survival periods of more than 2 years from the time of admission are rare in any event in unequivocal cases of osteogenic sarcoma).

Post-amputation follow-up studies in some of these cases showed in the first place that when the phosphatase value had been distinctly high, it promptly dropped, sometimes even to a level normal for the age of the subject. Furthermore, there was not necessarily a distinct rise from this level when metastases were first manifest roentgenographically. However, subsequent values, especially if obtained only a few weeks or months before death, were always well above the normal, and in one case reached 94 units.

Other Tumors Primary in the Skeleton: Conditions such as giant-cell tumor, benign chondroblastoma, solitary benign enchondroma, chondrosarcoma (not much calcified or ossified), and solitary osteo-chondroma never elevate the alkaline phosphatase value of the serum. Ewing sarcoma does not do so either, even after it has become widely disseminated through the bones of the body, provided that there are no significant metastases to the liver. Of our seven cases of multiple myeloma, there were six in which the phosphatase values were strictly within the normal limits for adults, ranging between 1.8 and 3.5 units.

[†] Pul metastases suspected.

In the remaining case, the initial and subsequent alkaline phosphatase values were somewhat elevated. In this case (confirmed by autopsy) 20 determinations were made in the course of a year, and the values were always found above normal. The value was 5.1 on initial examination, reached a peak of 9.7 within 2 months, dropped irregularly during the subsequent 9 months to 4.2, and rose again to 6.4 shortly before death. In the liver, only one metastatic lesion, 0.5 cm. in diameter, was discovered, and this would hardly suffice to explain the increased phosphatase value in this one case, which has been more fully discussed elsewhere.¹²

Tumors Metastatic to the Skeleton: Unless these provoke bone formation—that is, unless they are osteoplastic—they do not tend to raise the alkaline phosphatase value. Thus, in a case of carcinosis in which the skeletal metastases are extensive but solely osteolytic (and by chance the liver is spared) the alkaline phosphatase value would theoretically be normal, or at most very slightly increased by the effects of callus formation around fractures. If on subsequent examination in such a case the alkaline phosphatase value was found to have risen say to 10, 15 or 25 units, one could prognosticate that autopsy would certainly reveal more or less extensive metastases to the liver, even in the absence of clinical jaundice or an increase in the serum bilirubin.

As to the cases presenting osteoplastic metastases (including cases of prostatic carcinoma—see also below) these are associated with definite though not necessarily dramatic rises in the alkaline phosphatase value. Specifically, in these cases, in the absence of metastases to the liver, the alkaline phosphatase is often not elevated to above 8, 10, or 15 units, even if the extent of the osteoplastic metastases is considerable. However, in one case (that of a woman of 37) the alkaline phosphatase value rose during the month before death, from about 56 units to 85 units. Autopsy revealed that the carcinoma was primary in a bronchus, while the liver contained only a few pinhead-sized metastases, so that the dramatically high values in this case can safely be ascribed almost solely to the osteoplastic metastases, which involved nearly the entire skeleton.

Systematized Anomalies of Skeletal Development: Among these, one is quite likely to find a definite elevation of the alkaline phosphatase value in fibrous dysplasia of bone¹³ (if the extent of the skeletal involvement is considerable). In two such cases, we obtained values of 17.1 and 22.6 units respectively. Sometimes these cases are mistaken clinically for instances of hyperparathyroidism, but aside from clear-cut clinical

differences between these two conditions it may be pointed out that in fibrous dysplasia of bone the calcium and inorganic phosphate values of the serum are within normal limits. In cases of osteopetrosis (marble bone disease) the phosphatase value may likewise be increased. In one case—that of a boy of 16—the value on admission was 21.3 units. In cases of osteogenesis imperfecta the value may be found raised above the normal for the age of the subject if fractures are present. In none of a number of cases of multiple exostosis, skeletal enchondromatosis, and achondroplasia did we find elevations of the alkaline phosphatase value of the serum.

SIGNIFICANCE OF INCREASED ALKALINE PHOSPHATASE VALUES IN SKELETAL DISEASE

After this survey of the various skeletal disorders showing increases in the serum alkaline phosphatase value, it seems appropriate to crystallize and restate the common factor apparently underlying the elevation. This factor seems to be the new formation of some kind of osseous tissue in connection with the disorder.

On the basis of this idea, one can understand why the serum alkaline phosphatase value should be particularly high when there is extensive Paget's disease, since in that disease the reactive formation of new bone is unusually lively, although the osseous tissue formed is not normal. On the same general basis, one can understand why this value is particularly high in moderate or severe rickets, even though in this disorder the osteogenic reaction is expressed in the formation only of osteoid and not of true bone. Again, in hyperparathyroidism the demineralization of the bones is associated with reactive scarring and new bone formation, and accordingly with a rise in the phosphatase value. On the other hand, in uncomplicated cases of senile osteoporosis and menopausal osteoporosis, in which even devastatingly severe thinning of the bones is usually not associated with reparative new bone formation, the phosphatase value tends to remain at normal levels. Correspondingly, in those tumorous disorders in which the skeletal lesions are purely lytic (multiple myeloma, for instance) the phosphatase value is usually also not above normal. In those tumorous disorders in which the skeletal lesions are osteoplastic (osteogenic sarcoma, osteoplastic carcinomatous metastases) the phosphatase value is likely to be raised.

Altogether, these examples seem to suffice to show that the new

| | TABLE II | | | | | | | | |
|-------|----------|--|--|--|--|--|--|--|--|
| CASES | тои | CARCINOMA OF PROSTATE AND SHOWING HIGH ALKALINE E VALUES | | | | | | | |

| · No. | Acid# E | Alk # E | No. | Acid # E | Alk# E |
|-------|------------|------------|-----|-------------|-----------|
| 1 | 0.2 | 7.0* | 6 | 0.1 | 18.3* |
| 2 | 0.3 | 10.4‡ | 7 | 0.4 | 25.6‡ |
| 8 | 0.5 | 12.0‡ | 8 | 0.3 | 27.27 |
| 4 | 0.3 | 14.9* | 9 | 0.6 | 94** |
| 5 | 0.3 | 16.0‡ | 10 | 0.5 | 121* |

[·] Paret's disease.

formation of osseous tissue in connection with skeletal disorders is the factor positively correlated with the rise in the alkaline phosphatase value. Corroboratively, the healing of a skeletal disorder (for instance rickets or hyperparathyroidism) through appropriate therapy is associated with a decline of the phosphatase value to the normal level, in harmony with the cessation of the abnormal reactive osteogenesis.

RANGE OF VALUES FOR SERUM ACID PHOSPHATASE

As determined by the Bodansky method, the normal range of serum acid phosphatase values (for children and adults of both sexes) can be stated as lying between 0.1 and 0.4 units per 100 cc. As determined by the Gutman method, the corresponding values are 0.5 and 2.5 units. About 90 per cent of hospitalized subjects without prostatic disease show values within the indicated normal ranges by both methods. Values above 0.8 units by the Bodansky method and 10.0 units by the Gutman method must be regarded as definitely abnormal and specifically as indicating the presence of prostatic carcinoma which has metastasized.

The values falling within the intermediary or doubtful zone (0.4 to 0.8 units and 3.0 to 10.0 units respectively by the two methods) raise some questions. First of all, as shown by Table II, acid phosphatase values* within this range are obtained not infrequently in cases showing

t Cirrhosis of liver.

¹ Carcinoma with extensive metastases.

^{**} Osteogenic sarcoma with extensive metastases

[#] E == Phosphatase.

From this point on, unless otherwise indicated, the values will be given in terms of Bodansky units only.

| | TABLE III | | |
|--------|-------------|----|----------|
| BENIGN | HYPERTROPHY | OF | PROSTATE |

| Age | Acid # E | Alk# E | Age | Acid E | Alk E |
|-----|-------------|-----------|-----|-----------|----------|
| 67 | 0.1* | 3.3 | 70 | 0.3 | 5.5† |
| 57 | 0.2 | 3.6 | 78 | 0.3 | 1.9 |
| 63 | 0.2* | 2.0 | 63 | 0.4* | 2.3 |
| 82 | 0.2 | 2.9 | 63 | 0.4* | 2.1 |
| 65 | 0.2 | 4.8 | 76 | 0.7* | |

^{*} Tissue examination showed fibroadenomatous hyperplasia.

E == Phosphatase.

TABLE IV

CASES OF PROSTATIC CARCINOMA WITHOUT OR
BEFORE ORCHIECTOMY

| Case No. | Acid = | Alk # E | Metastases by x-ray | Case No. | Acid # E | Alk # E | Metastases by x-ray |
|-------------|--------|------------|------------------------|-------------|-------------|------------|------------------------|
| 1 | 0.3 | 29 | Absent | 6 | 10 | 4.1 | Absent† |
| 2 | 0.4 | 6.7 | | 7 | 2.6 | 12.3 | Present |
| 3 | 0.7 | 3.3 | Absent | 8 | 3.3 | 4.1 | |
| 4 | 0.8 | 8.8 | Present* | 9 | 12.8 | 14.6 | Present |
| 5 | 0.8 | 9 1 | | 10 | 30,2 | 8.5 | Present |

^{*} Negative 3 months before this value was obtained (at which time the alkaline E was 2.3 u.) but positive 4 months after it was obtained.

high alkaline phosphatase values and not representing carcinoma of the prostate. Indeed, three of the ten cases shown in this table had values falling within the doubtful range and specifically of 0.5, 0.6, and 0.5 units respectively. Values within the doubtful range are also obtained in similar cases by the Gutman method. Furthermore, in our experience, an occasional instance of benign hypertrophy of the prostate may also yield values within this range, as shown in Table III. Finally, it must be pointed out that as shown by Table IV, some proved cases of carcinoma of the prostate show acid phosphatase values not only within the doubt-

[†] Osteoporosis due to nutritional deficiency.

[†] Clinically, the tumor had already extended to the periprostatic soft tissues

[#] E = Phosphatase

ful, but even within the normal range. In this respect, also, our experience is in harmony with that of others.

SERUM ACID PHOSPHATASE VALUES IN CASES OF PROSTATIC CARCINOMA

Table IV shows data on ten cases of unequivocal carcinoma of the prostate without orchiectomy or before orchiectomy. The cases are arranged in increasing order of the acid phosphatase values. In the first two of these cases, these values are within our normal range. In the third case the value (0.7) is in the doubtful range. In the other seven, it is in the abnormal range, reaching, in one case, the extreme value of 30.2 units (roughly 100 times the normal average).

In regard to five of these last seven cases, we have data as to whether or not metastasis was present roentgenographically in the pelvis and neighboring bones. In the four in which we know it was present, the high acid phosphatase value was associated with some rise in the alkaline phosphatase value. In the fifth case, in which we know it was not present, the surgeon (Dr. Paul Aschner) informs us that clinically the tumor, while already metastatic, had apparently extended only to the periprostatic soft tissues. In this case, the alkaline phosphatase value (4.1 units) was at the upper limit of the normal. Thus, these cases confirm, in the first place, what has already been established by Gutman, by Barringer and Woodard,14 by Huggins and Hodges,15 and by others on the basis of much larger series-namely, that when the carcinoma breaks the bounds of the prostate and metastasizes to the regional tissues and to the skeleton, the acid phosphatase value of the serum usually rises to an abnormal level. This rise is due to the fact that the acid phosphatase secreted by the prostatic tumor tissue is entering the circulation in large amounts. Furthermore, these cases show again that the osteoplastic response of the skeletal tissues to the metastases is the factor responsible for the rise in the alkaline phosphatase value of the serum. On the other . hand, these conclusions are corroborated by the findings in our cases showing low or only doubtfully elevated acid phosphatase values. In only two of our three cases of this kind do we have roentgenographic data on the presence or absence of metastases. However, in both of these, skeletal metastases were absent, and in both again the alkaline phosphatase level was within normal limits.

Table V presents a series of acid and alkaline phosphatase determinations in a case of carcinoma of the prostate in which both of these values

| TABLE V | | | | | | | | |
|---------|----|-----------|----|----------|---------|----|-------------|--|
| CASE | OF | CARCINOMA | OF | PROSTATE | TREATED | BY | ORCHIECTOMY | |

| Date | Acid # E | Alk # E | Date | Acid # E | Alk # E |
|---------|-------------|------------|---------|-------------|------------|
| 3/12/41 | 2.6* | 123 | 4/7 | 0.1 | 3.7 |
| 6/30 | Orchie | ectomy | 6/30 | 0.4 | 3.4 |
| 8/ 1 | | 19.5 | 11/8 | 1.2 | 64 |
| 11/5 | 0.5 | 5.2 | 1/11/43 | 1.4 | 12.6 |
| 12/3 | 0.4 | 3.4 | 3/19 | 1.0 | 14.6 |
| 1/ 5/42 | 0,3 | 3.2 | 4/5 | 1.1 | 17.6 |

^{*} Metastases to skeleton apparent in x-ray films. # E = Phosphatase.

were high and metastases to the skeleton were already apparent in the x-ray films before performance of a therapeutic orchiectomy. This case has been followed for 21 months after orchiectomy. Though unfortunately we lack, in this case, an acid phosphatase determination to go with the first alkaline phosphatase determination after orchiectomy, yet the data illustrate the usual postoperative course of these values in such cases and are particularly valuable on account of the long period covered. Postoperatively (as we know from other cases) the acid phosphatase starts to decline sharply, and concomitantly the alkaline phosphatase rises. The latter then also starts to decline. In the case shown in the table, 8 months postoperatively, the acid and alkaline values had both gone down to normal (0.1 and 3.7 units respectively). Some months later, however, they had both begun to rise again-the acid value first and even more steeply than the alkaline-and on the last examination-21 months after the operation-the acid value was 1.1 units and the alkaline 17.6 units.

In connection with the course of the phosphatase values in this case, the course of the changes in the roentgenographic findings is interesting. The immediate postoperative rise in the alkaline phosphatase value was associated with a prompt increase in the osteoplastic reaction to the metastases in the pelvic bones. Specifically, areas which previously had not appeared osteoplastic roentgenographically soon did appear so, the pelvic bones having become much more extensively radiopaque than

they had previously been. Some months later, when the acid and alkaline phosphatase values had dropped to normal levels, the roentgenogram showed substantial decrease in the radiopacity of the pelvic bones. Again some months later, with the return of the acid and alkaline phosphatase to high abnormal values, the pelvic bones are again showing pronounced and extensive opacity roentgenographically.

It is not possible to be certain about the explanation of this series of changes in the postoperative roentgenographic pictures. It may be surmised that the immediate effect of the orchiectomy upon the tumor rissue proper in the pelvic bones was to arrest its growth, and that this arrest was associated with an osteoplastic reaction tending to crowd out the tumor tissue more completely. After the metastatic tumor tissue had become more or less choked off in consequence, the osteoplastic reaction tissue apparently began to be resolved. Subsequently, the checking influence of the orchiectomy upon the residual tumor tissue in the pelvic bones would seem to have weakened, and, in association with the consequent regrowth of the tumor tissue, there was an intensification of the osteoplastic reaction to it.*

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This patient, who was on the urological service of Dr. Paul Aschner, and on whom Dr. Isidor Palais did the orchiectomy, has since died and come to autopsy. Death occurred on June 14, 1943, 23½ months after the orchiectomy. It may be profitable to summarize the total picture which has thus now become available. Concomitantly with the return of the alkaline and acid values to within the normal range after the orchiectomy, there was a pronounced improvement in the general and local clinical status. Indeed, in regard to the latter, whereas prior to orchiectomy the tumorous prostate was very large and hard, eight months after it, Dr. Aschner noted that the right lobe was of normal size while the left lobe was also small though it was nodular at its apex. Concomitantly with the subsequent new rise in the acid and alkaline phosphatase values to abnormally high levels there was a definite and rapidly progressive recurrence of the prostatic enlargement. The patient was readmitted to the hospital on May 5, 1943, at which time a large boggy mass was found on the floor of the pelvis, surrounding the rectum. On May 11th, the acid phosphatase value was 1.8 and the alkaline phosphatase value 43 units.

At autopsy it was found that the local pelvic tumor mass, in which the prostate could no longer be distinguished as such, had infiltrated the floor of the bladder, the space of Retzius, and the peri-rectal tissues and had produced a so-called "frozen pelvis." Section of this tumor tissue showed it to be a highly anaplastic carcinoma. Tumor tissue was found nowhere else except in the skeleton, which was heavily involved. The metastases to the skeleton were all osteoplastic. It is worth noting that histologic examination of the bones indicated that, in the past, metastatic tumor tissue in them had undergone widespread necrosis. However, in addition to wide areas of necrotic tumor the sections also revealed a good deal of viable and actively growing carcinomatous tissue in the bones in the bones is that one of the unmediate direct

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LONG CALDERWOOD

The Birthplace of the Hunters

FENWICK BEEKMAN

of the spring of 1935, the author decided to visit the birthplace of William and John Hunter at Long Calderwood, an old farmstead situated but a short distance from the kirktown of East Kilbride, in Lanarkshire. The June day was warm and overcast and light showers of rain, ceasing as abruptly as they commenced, repeatedy obliterated the landscape with a curtain of film, to be followed by bright sunshine.

Starting early in the afternoon, our motorcar carried us across the Clyde by way of the new George V Bridge and thence through the old streets of what was formerly the town of Gorbells. The road then led us along the south bank of the river to Rutherglen, passing on its way the Glasgow Green upon the farther bank. Reaching Rutherglen, the highway turned toward the south and rapidly ascended some five hundred feet of the slope of the Clyde Valley to reach the brow of Dychmont Hill. Here an extensive view is obtained, not only of the Clyde and the City of Glasgow, but also, on a clear day, of Arthur's Seat in the suburbs of Edinburgh, Ben Lomond and the Peaks of Arran. Traveling a mile farther, the kirktown of East Kilbride was reached.

East Kilbride, seven and a half miles south of the City of Glasgow, is built upon the northeasterly edge of a richly cultivated plateau, stretching southward into the shires of Ayr and Dumfries. To the north and east, the land dips gently into the winding valley of the Clyde, on the banks of which, five miles distant to the east, stands the City of Hamilton. The surface of the surrounding country, with its rolling hills and dales, is rudely broken here and there by rugged, stony "craigs," which rise high above the fields. The land is fertile and green, for it is used for the pasture of sheep and cattle, or the cultivation of grain. Much of the old kirktown appears to remain in the same state it was two hundred years ago, except perhaps for a few modern cottages that have been erected here and there. On the eastern and southern sides of

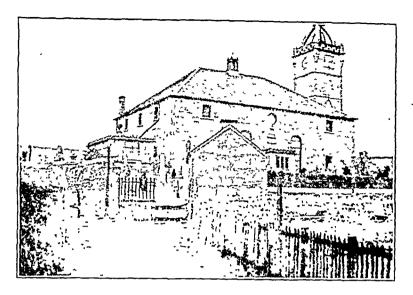


Fig. 1. Church at East Kilbride.

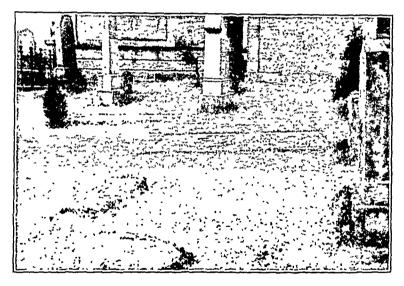


Fig. 2. Grave of John Hunter, Sr. and wife, Agnes Paul-(Flat stone, center).

a central square stand two rows of old stone-fronted buildings with gabled windows in the roofs and doorways opening directly upon the roadway. One of these buildings is said to have been the inn; the others may have contained stores with living apartments above. A narrow passage, paved with flagstone and nearly hidden from view between the two rows of buildings, leads the vistor directly to the "auld kirk." standing upon the brow of a small hill, its burying ground stretching gently down toward the east (Figure 1). The church, a simple, rec-

tangular, stone building with a slate roof sloping up from its four walls, has a square clock tower built against its north wall, which is surmounted by a Gothic crown or lantern which in design is much like that upon the tower of St. Giles' Cathedral in Edinburgh. The well-kept burying ground, surrounded by a stone wall with iron gates guarding the two entrances, contains ancient gravestones and a "watchers' house," where vigil was kept against the marauding of "resurrection men." Close to the east wall of the kirk, lies a flat, brownstone slab (Figure 2). The carved inscription upon its weather-beaten surface, though dulled by age and filled with lichen, can still be read.

THIS IS THE BURIE
ALL PLACE OF IOHN
HUNTER OF CADER
FEILD* AND AGNES PA
UL HIS SPOUSE

1751

This John Hunter, grain merchant of East Kilbride, was born during the early years of the reign of Charles II, probably in the year 1663, and on December 30th, 1707—at the age of forty-four—married Agnes Paul, a handsome, talented lass twenty-two years his junior, the daughter of Baillie John Paul, a malster of the City of Glasgow. John Hunter took his bride to East Kilbride where they lived for ten years, during which time she bore him six children. At the age of fifty-four, John Hunter reached the important decision to withdraw from the laborious business of merchant and retire to what he thought would be the more leisurely life of a farmer. He therefore purchased a farm, it is said for the sum of £147, upon which he built a modest dwelling. To this simple home he moved with his wife and four children, for two of the six children born in East Kilbride had died during their infancy.

Entering our motor again, we left the kirktown behind and traveled northeast along Hunter Street, an old country lane bordered with thick hedges. Long Calderwood, the house that John Hunter built for his family, is approximately one mile distant from East Kilbride. The visitor, as he approaches, easily recognizes the homestead from some distance, almost hidden by trees, situated on the left hand side of a gentle

The use of Calderfield instead of Calderwood is explained by Mather as follows: "the parish was then divided into townships, hamlets or clackans; Calderfield being the name of the township, and Calderwood the biggest house in it, the whole came to be recognized by the latter name."

curve in the roadway as it turns to the east toward Blantyre, on its winding way to Hamilton, five miles distant. The original dwelling has been, without a doubt, slightly altered, but the farm buildings appear to have been added to extensively during the two centuries that have elapsed since the "laird" of Long Calderwood first erected his farmstead.

William Hunter inherited Long Calderwood upon the death of his brother James, in the year 1745, and added to its acreage. In a letter to his friend William Cullen, on August 6th, 1754, he wrote: "I know you'll say another letter from Hunter! What the devil is he about now? Why, I am going to buy land: the first time this has ever entered into my head. In short, Mr. Fleming of Nook, in Kilbryde, writes me that Mr. Borland is going forthwith to sell his land in Longcalderwood. It lies entiguous, you know, to what was my father's and the two together make a vote in the county. If I could get it, both would be as easily managed as one, and should it afterwards be expedient, both might be sold with the same trouble as one. Besides, I cannot get it out of my head that I shall one time or other live there, and, in that case, I should like to possess both, that I might have a little bit all around me that I could call my own, and to give you a vote, or any of your friends that should stand for the county member." Though the owner of Long Calderwood for thirty-eight years, William Hunter, it seems, found the opportunity of visiting it only once, in 1750, just before his mother's death. At present "the estate," Sir Arthur Keith informs us, "comprises 177 acres." William Hunter willed the property to his nephew, Matthew Baillie, on his death in the year 1783, having become estranged from his brother John. Baillie, however, recognizing the injustice of this act, deeded the property over to his younger uncle. John Hunter owned Long Calderwood for ten years but never visited it during this time and, when he died in the year 1793, the farmstead returned again to Matthew Baillie. Since then it has been continuously in the Baillie family and this may well account for the excellent condition in which the old farmstead is found today.

John Hunter, Sr., built his house facing the south, on the north side of the road, the rear overlooking cultivated fields that stretch toward the valley of the Clyde. The house and connecting farm building (Figure 3), substantially built of roughly hewn stone, but now stuccoed.*

^{*} A photograph of the homestead, taken by Annan of Glasgow in the year 1885, portrays the house and connecting building before the walls were stuccoed.

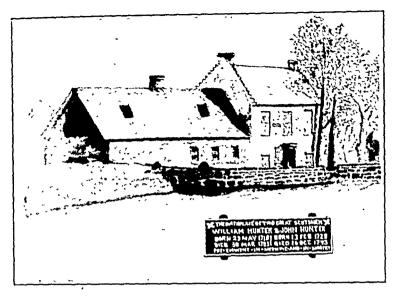


Fig. 3 Long Calderwood (Author's pencil sketch).

are separated from the road by a narrow strip of terraced lawn behind a low stone wall. The dwelling portion, two stories high, is square in shape, with gabled ends that rise above the level of the roof and are cut with corbie-steps leading up to square, squat chimneys placed at either end of the peak of the slated roof, which may be assumed to have replaced one of thatch. The long, low farm building, in size out of all proportion to the dwelling, extends from the west gable forming, with other stone out-buildings, a farmyard in the rear. This is entered from the highway by a wagon road, spanned by stone gate-posts, to the west of the farm-building. "The long low stone building which abuts on the western gable of the house," writes Sir Arthur Keith, "provides a scullery, a 'bothy' and stabling for five horses, is clearly of later date; so is the small coach-house and great cow-byre behind the dwellinghouse. But the barn, with its loop-holed and slotted end towards the road, its doorways on opposite walls, between which the corn was threshed by flail and winnowed by hand-is certainly part of the farmsteading which John Hunter's father built."

The front of the dwelling has three large windows, giving sunlight to the bedrooms on the upper floor; while the main entrance, a narrow doorway within a small porch, reached by two stone steps, with a window on either side, opens upon the ground floor. A tablet, more recently placed upon the wall to the right of the porch and on the level

of the upper windowsills, commemorates the birth in this humble home of the two illustrious Scotsmen.

The visitor, on entering the dwelling, finds himself within a narrow passage running from left to right. Directly in front of him, ascending to the left, is a narrow stone stairway leading to the floor above. To the left is the kitchen, a room some fourteen feet square, with a door opening into the "bothy," where the farm help slept, and containing a spacious fireplace, once holding crane and spit but now occupied by a common cook-stove. To the right the passageway gives entrance to a room of much the same dimensions as the kitchen, with a window opening to the south and another to the east. Though now a parlor, an alcove with sliding panels built against the north wall and containing two beds denotes that the room was used at one time as a sleeping apartment. Behind the stairway and between this room and the kitchen, is a third. little larger than a closet, that was probably used as a chamber for one or more of the numerous children of the family. The upper floor is laid out in like plan to that below. The chamber above the kitchen is said to have been occupied by the parents and here the four youngest of the family, it is assumed, were born.

The four children, brought to Long Calderwood by their parents in the year 1717, were John age nine, Janet age four, James age two, and Agnes age one. Less than a year after taking residence on the farm, their seventh child and fourth son was born, on May 23rd, 1718, and was named William. Dorothy was born January 26th, 1721 and, a year later, their eldest child, John, died on February 27th, 1722. Isabel was born December 7th, 1725 and finally two years later, on February 14th,*
1728, the last-born of the aging couple arrived and was named John.

At the time of this important event John Hunter, Sr. was at least sixty-five years of age and his wife forty-three. Besides the infant "Jock," there were six other children, Janet the eldest being fifteen years of age, James thirteen, Agnes twelve, William ten, Dorothy seven and Isabel two. It was a happy family, the children having an intense devotion for their parents, especially their mother, as well as for each other. Mrs. Hunter was an outstanding woman of strong character, if

There has been considerable discussion as to the exact date of John Hunter's birth. Drewry Ottley states that John Hunter used February 14th for his birthday and the Royal College of Surgeons (Eng.) has chosen this day for the celebration of the anniversary of his birth. The parish register at East Kilbride gives February 13th, 1728 as the day of his birth and his baptism on March 30th. An old Bible, formerly the property of James Hunter, puts the date as February 7th and a contemporary notebook, formerly owned by Miss Hunter Baillie, states that John was born on the 9th. Everard Home gives the date as July 14th; this, however, must have been a typographical error. Stephen Paget says, "Probably he was born during the night of the 13th-14th."

we can judge from the little that is known of her, possessing deep affection, lasting patience, and untiring will and a great deal of common sense. During her youth in Glasgow, Agnes Paul had received an excellent schooling and had acquired many of the lady-like accomplishments of the time, for she was the daughter of a man of means and of importance in the community, who was not only a Magistrate but also held the honorary office of Treasurer of the City. Her married life had heen hard, for it was no easy task to bear ten children, to care for them, keep house and assist at the dairy work on the farm. Her ambition for her children's careers, however, does not appear to have been dampened by the hard work and many worries which we shall see were ever present, for it seems she found time to train them in polite manners, gentlemanly and ladylike customs, as well as the accomplishments that she had acquired during her younger days. The "laird," John Hunter, Sr., appears to have been a man of intelligence, patience and industry, who had in all probability received a grammar school education and possessed at least a desire for some of the cultural pursuits. Observing his portrait, painted about the year 1740 by his son, James, shortly before his death, which now hangs in the halls of the Royal College of Surgeons (Eng.), we perceive an old man. The features of his smoothshaven face, though clean-cut and full of character, appear careworn. The mouth, with thin, tightly closed lips and prominent jaw, denotes determination and the eyes, though kindly, possess a peculiar, piercing quality that commands respect. His grandson, Matthew Baillie, said "he was a man of good understanding, of great integrity and of an anxious temper."

The life on this small farm was in all probability a busy one, for neither of the parents were shiftless and there was little if any money to spare for hiring help on the farm or in the house. It may be presumed that "Jamie" and "Willie." when not attending the grammar school at Fast Kilbride, were called upon to assist their father in the fields or tending the herd. Janet was certainly mature enough to relieve her mother of some of the house and dairy work and "Nannie" (Agnes) no doubt was intrusted with the care of her two little sisters "Dollie" (Dorothy) and "Tibbie" (Isabel) and perhaps with baby "Jock." There is childish fancies, by his mother and four sisters, from the time of his birth; and shortly, as we shall see, he was deprived of the companionship

of his elder brothers, whose presence might have strongly influenced his early training and thereby counteracted the coddling of the feminine members of the family.

Mr. Hunter appears to have desired that his sons should not enter "trade" as he had done and, consequently, planned to educate the two older ones, who were now finishing grammar school, where they had shown exceptional ability, for professional lives. In order to accomplish this, further sacrifices had to be made by the parents. We find that the herd boy was dispensed with a year before "Jockie's" birth and a year after fifteen acres of land were sold in order, it is said, to settle the payment on an indenture, to a writer of the Signet in Edinburgh, for "Jamie," who was now fourteen years of age, was to study law. Two years later, in the autumn of the year 1731, "Willie," now thirteen years of age, a small, slender lad, frail in frame with delicate features much like those of his father, entered the "College" at Glasgow to study for the ministry in the Scotch Kirk; having obtained a bursary of the Bajan* Class to the amount of £ 10 per annum for four years, although the curriculum required for graduation called for five years attendance.

Coming under the influence of that great secular scholar, Francis Hutcheson (1694-1746), who held the Chair of Moral Philosophy, William Hunter soon developed a spirit of scepticism about what he was taught and a desire to learn through inquiry. Buckle, in his History of Civilization in England, writes that: "By his lectures, and by his works, he [Hutcheson] diffused a taste for bold inquiries into subjects of the deepest importance, but concerning which it had previously been supposed nothing fresh was to be learned; the Scotch having hitherto been taught, that all truths respecting our own nature, which were essential to be known had been already revealed." Having finished his five years of study, William discovered that he was unsuited for the ministry and declined the office in the Church and, in consequence, did not receive a degree.

Returning home in the summer of 1736, he joined a young practitioner at Hamilton, a friend of the family, named William Cullen (1710-1790), as an assistant. A lasting friendship ensued and later in life William Hunter often acknowledged that these "were the happiest years of my life." Residing with Cullen until the autumn of 1739,

^{*} Mather informs us that "The term Bajan was employed in the French and Scotch Universities, and is evidently a corruption of bec jaune (yellow beak), an expression meant to designate a nestling or unfledged bird.

William Hunter then went to Edinburgh in order to attend the lectures of Alexander Monro on anatomy, and in the following year he sailed from Leith for London, in order to obtain further study in preparation for undertaking the surgical part of the practice, as a partner of William Cullen at Hamilton.

During William Hunter's absence, the tranquility of Long Calderwood was rudely interrupted by a series of unhappy events, that have been dramatically chronicled in intimate letters addressed to him in London. These reveal the deep affection that existed between the members of this humble family, residing on the small farm in Scotland, and gives us a glimpse of their stalwart characters and simple faith in God. The first of the letters vividly pictures the poignant grief occasioned by the untimely death of Agnes, a favorite sister but particularly dear to the elder brother James, the author of this pathetic epistle. Her death occurred on March 13th, 1741, while away from home, accompanying her brother James who had taken his sister with him to a neighboring town where he was to exchange a farm horse. Mounted behind her brother, though weakened by the ravages of pulmonary tuberculosis, "Nannie" and "Jamie" set forth upon their fateful journey; but before traveling far on their way, the brother realized that all was not well. In his narrative to William, he wrote: "we no sooner allighted from our horse when she complained of a faintness great weakness and cold feet: with the little assistance I could give her she sat there pretty easy for 2 hours, we mounted our horse again for Hamilton, . . ., but before we had got the length of a Gun shot away, she grew so weak that I was obliged to turn back, after giving orders to the Good wife about her I rode to Hamilton post haste and brought Dr. Cullen out with me, by this time she had got to bed and was tolerably easy but extreamly weak, ..., we got a Car and put a bed upon it, and he took her in his arms and layd her gently down upon it, it put me in mind of the poets bringing Eleonora into the Sun to take her last sight and farewell of the world, she was no sooner laid down but she complains of her faintness occasioned by the fatigue of coming out. Mr. Cullen found she could not make it out, takes her up again in his arms to carry her in, there she resigned her young and tender soul. I was thunderstruck with such an unexpected mournful sight, nor will I ever forget that approving nod she gave me the moment she dyed. I gave myself up to the most violent grief which I had all along stiffled upon her account, and the Doctor,

instead of comforting me, had me indulge it to the utmost..."

"I would not advise you to stiffle your grief, no, my dear Will, indulge it heartily, give it the loosest reins the more impetuous it is, the better 'twill sooner satiate itself.... When I cast my eye upon that better 'twill sooner satiate itself. . . . When I cast my eye upon that Blanck made be (wixt) you and me, which but a little while agoe our dear sister filled, methinks it looks a gloomy dismall vacuum." And in closing his letter he wrote: "Take care of your health my Dr. Willic, forget not to pray to Nannie, imagine you have a sister in Heaven who is as able, I hope, as willing to hear and do for her friends here; . . .

Three months later William Hunter, having received an offer to become the assistant of Dr. James Douglas (1675-1742), made up his mind to remain for an indefinite period in London. The news of this decision appears to have precipitated considerable consternation within the family at home, as revealed through the contents of a letter written to "William" by his aging father, dated 28th July 1741:

"Nothing has proved a greater comfort than the hopes of seeing you here soon; but your letter has cast a very great damp upon us all. I think you have been in a very extraordinary manner obliged to Dr. Douglas, and whatever opinion I may have of his present offer, or however unwilling I may be to consent to it, still I must thankfully own it, as a particular instance of his kindness to you. I surely must soon expect

as a particular instance of his kindness to you. I surely must soon expect to be beyond this side of time, considering my age and present indisposition, being for some days past confined to my bed with sickness, and a severe fit of the gravel, and would be glad to have you near me for the little while I shall be in this world; though at the same time I should be sorry to hinder you from making your way in the world, the best way you can.—I wish you to consider well what you do.—With Dr. Cullen you may be very comfortably settled, and make money, and if you miss this opportunity now, you cannot be sure of it at another time -Dr. Douglas's kind offer is only for a time. He may die before you come home or are settled, and leave you without friends at a great enough uncertainty. I suppose now you know very well the difference between the expence of living at home and abroad, and that perhaps cloaths and pocket-money may cost you more than your whole expense at home would do. You know my willingness to assist you, but you know too, that already I have gone fully as far as my numerous family will allow of.—You must now do something for yourself. Consider all these things, and if you can persuade me that it is for your good, I will

not be against it."

The prophetic words written by the old man were shortly realized, for John Hunter, Sr., died October 30th, in the same year (1741), at the ripe old age of seventy-eight.

James, though he now became the nominal head of the family, did not remain at home for long. Sir Everard Home tells us that he "was brought up to the law, as a writer to the signet in Edinburgh, but in the year 1742 [probably late in the year 1741] went to London on a visit to his brother William, who was at that time a teacher of anatomy, and so much was he captivated by the pursuits in which he found his brother engaged, that he purposed to follow them himself, and become a practitioner in physic.* His health however was so much impaired by his application to anatomy, that he was obliged to return to Long Calderwood, where he died of a spitting of blood, in the twenty-eighth year of his age [April 11th, 1745]."

During James's sojourn in London with William, another tragedy was occurring at Long Calderwood; for the brothers received news that Isabel, their youngest sister who was only sixteen years of age, was ailing; and William wrote his mother, giving advice, encouragement and sympathy. "I am heartily concerned for my dear little sister Tibbic, but I hope the Mare's milk and the Fole together will surely recover her, for you know she likes Foles and Calfs. Tell her she must write me about the White Hamilton Stork [stirk?], and that Jamie and I will pay her a visit as soon as we have got our pockets full of gold to buy her a country seat, and give her what horses and other things she wants." Hardly had this letter reached Scotland before death came to "Tibbie," on July 30th, 1742; the third to occur in this home during the short period of a little over a year.

There were now only four left at home; Mrs. Hunter, Janet, Dorothy, and "Johnnie." Janet married a ne'er-do-well named Buchanan, some time during the year 1748. "This marriage gave the family great concern;" wrote Sir Everard Home; "for the qualities which had rendered Mr. Buchanan agreeable, led him into dissipation, and made him neglect his business."

John Hunter was thirteen years old when his father died; a sturdy, heavily built, red-haired lad less than five feet in height, with a de-

[&]quot;The late Dr. Hunter has been heard to remark, that if he [James] had lived to practice physic in London, nothing could have prevented him from rising to the top of his profession." (Home)

termined jaw, who enjoyed outdoor life and despised school. "He was sent to grammar-school," wrote Sir Everard Home, "but not having a turn for languages, nor being sufficiently under control, he neglected his studies, and spent the greatest part of his time in country amusements." He was self-willed, short-tempered and given to tantrums ending in tears, when crossed in some desire. Joanna Baillie, his niece, wrote that "he was extremely indulged, and so humoursome that he would often, when a pretty big boy, sit for hours together crying when he could not get what he wanted; and could not be taught to read but with the greatest difficulty, and long after the age when other children read English fluently." I think, today, it would be said that he was emotionally unadjusted. "Jock" was taken from school by his fond and indulgent mother soon after her husband's death in order, it is said, that he might help on the farm, as both James and William were away in London and Dorothy alone remained. This, in all probability, was to the liking of "Jock" who, it seems, had little respect for the subjects taught at school and enjoyed roaming through the countryside.

"When I was a boy" [he said in later years] "it was a little reading and writing, a great deal of spelling and figures; geography which never got beyond the dullest statistics, and a little philosophy, and chemistry as dry as sawdust, and as valuable for deadening purpose. I wanted to know about the clouds and the grasses, why leaves changed colour in the autumn. I watched the ants, bees, birds, tadpoles, and caddis worms. I pestered people with questions about what nobody knew, or cared anything about."

From these remarks it becomes evident that even at this early age John Hunter possessed that insatiable curiosity and scepticism of mind which, in later life, gave him the endurance to push his inquiries until he obtained, to his own satisfaction, the correct solution of the investigation. As a helper on the farm, it is feared, he was of little assistance in the daily chores, but if there was a sick cow or mare in foal, we can be sure that the boy was in attendance and spared neither time nor inconvenience in doing what he could to help. Apparently all the members of the family were interested in animal life of both the domestic and wild creatures, but to "Jock" there seems to have been no other interest. All through his writings, in the *Philosophical Transactions*, in *Animal Oeconomy*, and in the *Essays*, edited by Sir Richard Owen, can be found abundant evidence of observations made during these

early years he spent at Long Calderwood. Like many another boy who has little or no interest in the subjects taught at school, the youthful John Hunter gave every available moment to investigating animal life and observing the habits of animals, birds, insects, and fish. Starting early in life, he developed an antipathy for the written word of authority and substituted inquiry for obtaining what he wished to know. It is hard to believe that he was a wayward boy, as some of his biographers seem to imply; but, being self-willed and determined in character, it appears he refused to learn in the accepted way at grammar school and chose his own method of acquiring knowledge through observation in the field of study that most interested his inquisitive mind. Discovering that inquiry was the really accurate method of learning the truth from nature, he soon lost respect for authors who made mere compilations from the books of older writers.

Reaching the age of twenty and having found no agreeable vocation, John Hunter decided to join his brother in London. Writing to William, he requested "that he would allow him to come to London upon a visit, making at the same time an offer to be his assistant in his anatomical researches; or if that proposal should not be accepted, expressing a wish to go into the army." His brother having accepted his offer, the young man set our during the early autumn of the year 1748 on his long journey to the Great Metropolis.

The following spring the two brothers in London were informed of their sister Janet's death, through a letter from their faithful friend:

Glasgow, 29th May, 1749

"My Dear Willie,

It is with pain I write to you, but it is to save your mother more pain in doing it herself. Your sister Mrs. Buchanan died Friday night last. It was after being valetudinary for some years; . . . Your mother and Dorothy, bating what they feel on this occasion, are otherwise well. I hope you will be very careful of your own health, that you may long be—what you will be while you live—a great comfort to them and to all your friends. I am, from the bottom of my heart, dear Willie, Yours William Cullen

William Hunter visited Long Calderwood for the last time during the autumn of 1750. The only occupants of the homestead were now his mother, whose health was rapidly failing, and his one remaining sister, Dorothy. We can be sure that at this time "Willie" renewed his old friendship with William Cullen, which after this was to be continued on to the year of his death only by means of an exchange of intimate letters and mutual acts of kindness; for these busy men were never to meet again. To his gratification, on October 24th the University of Glasgow saw fit to confer upon him the degree of Doctor of Medicine and, in the following March, his name was entered upon the "Roll" of the Faculty of Physicians and Surgeons of Glasgow.

"During this visit he shewed his attachment to his little paternal inheritance," wrote Simmons, "by giving many instructions for repairing and improving it, and for purchasing any adjoining lands that might be offered for sale. As he and Dr. Cullen were riding one day in a low part of the country, the latter, pointing out to him Long Calderwood at a considerable distance, remarked how conspicuous it appeared. 'Well'—said he, with some degree of energy—'if I live I shall make it still more conspicuous.'"

William Hunter surely must have found it difficult to leave his childhood home where his mother lay so ill, but pressing activities called for his presence in London where Mr. John Symonds, his assistant, with the help of John, whose anatomical knowledge was beginning to rival that of his brother, were conducting the classes during his absence. Though he must have realized that he was never to see his mother again, he undoubtedly obtained some comfort from the knowledge that she would be tenderly nursed by his sister, under the wise direction of his devoted friend. Six months later we find Cullen reporting to him on her condition. "Her ailments continue very obstinate . . .," he wrote, "I have endeavored to engage her in some exercise. She has tried going on horseback, and going in a cart and in a car, but every kind of motion raises her pain so much, that we cannot persuade her to repeat the trials. Upon the whole, I am persuaded some scirrhosity is forming in the stomach, which gives me a very disagreeable prospect with regard to her. She says nothing now about Johnie's coming down; but I know, in her present temper, it would have pleased her much if he had." Poor woman, she pined for the sight of her last-born, her "Jockie," before she died. However, this was not to be, for the practical William, writing from London, brusquely informed Cullen of his decision on this matter. "But I cannot consent this season to her request," he wrote, "for my brother's sake, for my own sake, and even for my mother's sake. It

would be every way a bad scheme. I have wrote of it to her, and I hope she will consider better of it, and find that it is really a whim begot of sickness and low spirits." Mrs. Hunter died November 3rd, 1751, at the age of sixty-six. Cullen, writing four weeks before this event, tells of her progressive weakness and advises William to delay no longer in writing to her or to Dorothy. "It gives some relief to Dorothy," he wrote, "that now your mother seems to be declining fast, it is with very little of those pains which formerly afflicted her." After assuring William that he would be present during his "mother's last moments" and arrange the funeral, he wrote-"my chief care shall be bestowed on. Dorothy. As you have no objection to my plan with regard to her, I shall do as I proposed, that is, as soon as your mother is interred, take Dorothy to my house, where I am sure she will find a very hearty welcome." William Hunter, in replying after his mother's death, expresses his satisfaction for the "kind attendance" of his friend during his mother's long illness and then discusses a plan for his sister's future. "Our next care must be about my sister;" he wrote, "who has recommended herself strongly to me by her indefatigable tenderness. Poor girl, I pity her from my soul. Your offer with regard to her is generous and friendly. I leave her to be determined by you and her friends. In the mean time, I would propose that she should stay in Scotland till the spring, both for the sake of good weather, and that my great hurry may be over, and that we may have some time to consider how our little affairs are to be managed in Scotland after she leaves the place. Then I should propose that she come up to me, or perhaps I may then send my brother to bring her." As far as we know, this plan was carried through. for John Hunter left for Scotland in the spring of 1752, as soon as the winter session at his brother's anatomical school was finished, and returned during the early autumn accompanied by his sister Dorothy, who was to reside with her brothers in the Great Piazza, Covent Garden.

We hear nothing further of anyone residing at Long Calderwood until the year 1778, when Dórothy, then a widow, returned to the old homestead with her two daughters. She had married the Reverend James Baillie, a minister at Shots, in 1758. Her daughter Agnes was born a year later and, on October 24th, 1760, a son was born, who was named Matthew. Soon after, moving to Bothwell, a town upon the Clyde near Hamilton, her second daughter was born on September 11th, 1762 and was named Joanna, for her uncle John Hunter. The family then moved

to Hamilton in the year 1769 and, when Dr. Baillie was appointed Professor of Divinity at the University in 1776, they moved to Glasgow. But his tenure of office in the "College" was short, for death claimed him two years later. Mrs. Baillie, with her daughters, then moved to Long Calderwood, her son having entered Balliol College, Oxford. During his vacations, Matthew studied anatomy at the Great Windmill Street School in London, where he won the respect and deep affection of his uncle, William Hunter, who taught him the art of observation and "communicated to him his love of science." His mother, at the time of her son's departure for the University, wrote her brother: "I have furnished him out in the best manner my situation could afford. I now give him over to you. Be a father to him—you the only father he has alive. I hope you shall never be ashamed of his conduct, but that he shall obey your directions in everything."

In the meantime Joanna, who had received her schooling in Glasgow, was beginning to develop great talents. She is said to have shown ability in music and drawing but, in addition, an exceptional aptitude for dramatics and composition. At Long Calderwood Joanna was thrown on her own resources; besides the outdoor life, where she came to know the country folk residing on neighboring farms, "her chief enjoyment was found in books."

After William Hunter died on March 30, 1783, Mrs. Baillie and her daughters moved to London to reside with her son, who had inherited his uncle's entire estate. Here Dorothy Hunter Baillie lived until her death, at a good old age, in the year 1807; to see her son become a great pathologist and the most outstanding physician of London, and her daughter Joanna rise to fame as a dramatist and poet, whom her friend Sir Walter Scott named "The Immortal Joanna."

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

April, I—The New York Academy of Medicine. Executive session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. The Eighteenth Hermann M. Biggs Memorial Lecture, under the auspices of the Committee on Public Health Relations; Malaria and Its Influence on World Health by Lieutenant Colonel Paul F. Russell, Medical Department, Army of the United States, Chief, Tropical Disease and Malaria Control Section, Division of Preventive Medicine, Office of the Surgeon General. Report on election of Fellows.

April 15—The Harvey Society in affiliation with The New York Academy of Medicine. The Seventh Harvey Lecture, "Sterilization of Air with Glycol Vapors," O. H. Robertson, Professor of Medicine, University of Chicago School of Medicine.

Max 20—The Harvey Society in affiliation with The New York Academy of Medicine. The Eighth Harvey Lecture, "Nutrition Under Wartime Conditions." V. P. Sydenstricker, Professor of Medicine, University of Georgia School of Medicine. ¶ Report on election of Academy Fellows.

April 2-Surgery, Program from the Surgical Services of the Goldwater Memorial Hospital. [Executive session-a] Reading of the Minutes; b] Nomination of Section Officers and one member of Advisory Committee. I Introductory remarks-Condict W. Cutler, Jr. TCase presentations—a] Extensive tuberculosis of the chest wall, operative result, Louis Carp; b] Disabling chronic arthritis complicated by acute gangrenous cholecystitis, cholecystectomy followed by cure of arthritis, Charles W. Lester; e] Block resection of sigmoid and adherent structures for carcinoma, with perforation and secondary abscess of

abdominal wall, George H. Humphreys (by invitation); d] Hyperthyroidism complicated by chronic cardiac disease, post-operative results, Grant P. Pennoyer; e] Cases illustrating a method of handling painful extremities in peripheral vascular diseases, Margaret Stanley-Brown; f] Gangrene of the lower extremity, supracondylar amputation under crymal anesthesia, Wilson E. Alsop; g] Arthritic hip joints, arthroplasty with the use of vitallium. cups, William A. Walker (by invitation). ¶ General discussion by W. Howard Barber.

Areil 6—Dermatology and Syphilology.

¶ Presentation of cases—a] From Beth Israel Hospital; b] From the Good Samaritan Dispensary; c] Miscellaneous cases. ¶ Discussion. ¶ Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee.

April 8—Pediatrics. [Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. [Papers of the evening—a] Delays in development of language in children, Samuel T. Orton; b] Emotional disturbances affecting speech, Frederick H. Allen (by invitation), Director, Philadelphia Child Guidance Clinic.

April 13—Combined Meeting. Neurology and Psychiatry and the New York Neurological Society. [Papers of the evening—Psychosomatic disorders—a] The historical and scientific issues in psychosomatic problems, Gregory Zilboorg; b] Physiological principles underlying psychosomatic disorders, Donal Sheehan (by invitation); c] The basis of classification of disorders from the psychosomatic standpoint, Lawrence S. Kubie; d] Psychosomatic diagnosis with special reference to cardiovascular syndromes, H. Flanders Dunbar. [Discussion—

Frank Freemont-Smith, Emanuel D. Friedman, Louis Leiter (by invitation), Bettina Warburg, Edward Weiss (by invitation), Philadelphia, Harold G. Wolff. ¶ Executive session, nomination of Officers and one member of the Advisory Committee of the Section.

APRIL 19-Ophthalmology. ¶ Instruction hour-7:30 to 8:15 oclock-Moving pictures. ¶Executive session-a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening-a) Peripheral retinal holes without detachment, Arnold Knapp; b] A case of chronic mercurialism exhibiting a colored reflex from the anterior lens capsule, Walter S. Atkinson. Discussion by Maynard C. Wheeler; c] Pathology following injuries of the eyes, Georgiana Theobald (by invitation); d] Unusual manifestations of malignant melancma of the uveal tract, Algernon B. Reese. Discussion by Bernard Samuels; el A combined intracranial and orbital operation for retinoblastoma, Bronson S. Ray, John M. McLean, Discussion by E. B. Burchell (by invitation), Bernard Samuels; f] Case report: Subconjunctival dislocation of the lens with sympathetic ophthalmia, Charles Perera.

April 20—Medicine. ¶ Reading of the minutes. ¶ Paper of the evening—The role of the internist in the management of sterility, William H. Cary (by invitation). ¶ General discussion. ¶ Executive session—Nomination of Section Officers and one member of the Advisory Committee.

April 21—Genito-Urinary Surgery. Reading of the minutes. Case reports—Medullary tumor of the adrenal—pheochromocytoma, Joseph Tenenhaum. Case reports of interesting renal malignancies invited. Paper of the evening—Classification of renal tumors, Meyer M. Melicow (by invitation). General discussion. Executive session—Nomination of Section Officers and one member of Advisory Committee.

April 21—Otolaryngology. Texecutive session—Reading of the minutes. Case presentations—a] Shrapnel in sphenoid sinus causing blindness, removal with recovery, Irving B. Goldman, Knut Houck (by invitation); b] Recurrent oncocytoma of the trachea, Arthur Palmer, Nathan Chandler Foot. Ceneral discussion.

Arms 16—Orthopedic Surgery. ¶ Reading of the minutes. ¶ Papers of the evening —a] Roentgen soft tissue studies in an orthopedic hospital, Raymond Lewis. Discussion by Stephen White; b] Ocular torticollis—differential diagnosis, Loren Guy. Discussion by Leon Lantzounis. ¶ General discussion. ¶ Executive session—Nomination of Section Officers and one member of Advisory Committee.

Arril 27—Obstetrics and Gynecology, ¶ Executive session-al Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Commitreport-Polyneuritis ¶ Case pregnancy, with review of the literature and a case report, Julius Lebovitz (by invitation). [Papers of the evening-a] Clinical evaluation of hysterography Morris A, Goldberger; b] A proposed annual textbook of gynecology. Each subject individually and compactly compiled in brief, concise and complete form. Facts on medications, etc. condensed for quick review. Pages and chapters illustrated by lantern slides, Robert J. Lowrie. TGeneral discussion.

May 3—Dermatology and Syphilology.

Presentation of cases—a] From the
New York Hospital and Cornell Medical College; b] From the Brooklyn Jewish Hospital; c] Miscellaneous Cases.

Discussion. Executive session—a]
Reading of the minutes; b] Election of
Section Officers and member of Advisory Committee—For Chairman: David
Bloom, For Secretary: George Morris
Lewis, For Member of Advisory Committee: Elias William Abramowitz.

May 7-Surgery, [Executive session-a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee-For Chairman: Louis Carp, For Secretary: Clay Ray Murray, For Member of Advisory Committee: John V. Bohrer. ¶ Case presentationsal Cholecystectomy. Subsequent choledochotomy and choledochoduodenostomy, two-year follow-up, Harold Keyes; b) Choledochoduodenostomy for recurring common duct infection and formation of stones, Thomas II. Russell; c] Endocholedochal sphincterotomy for dyskinesia, Ralph Colp; d] Primary carcinoma of the common bile duct, Radial resection, five-year follow-up, John H. Garlock. Papers of the evening-al Acute cholecytitis, present trends in treatment and why opinions differ, Henry F. Graham (by invitation); b] A five-year experience in biliary tract surgery, Pro. V. Prewitt. I General discussion-Grant P. Pennøyer, Philip D. Allen.

Max 12-Combined Meeting. Neurology and Psychiatry and Historical and Cultural Medicine. T Executive session-a Offivers and member of Advisory Committee elected for 1943-44; Section Neurology and Psychiatry-Chairman: Gerald R. Jameison, Secretary: Harold G. Wolff, Member of Advisory Committee: Charles Davison; b] Election of Officers and members of Advisory Committee; Section of Historical and Cultural Medicine-For Chairman: Edward F. Hartung, For Secretary: Paul E. Bechet; For Member of Advisory Committee: Herman Goodman. ¶ Paper of evening-Descartes and modern psychiatric thought, Iago Galdston, A. A. Brill. Discussion by Nolan D. C. Lewis and Tracy J. Putnam.

May 13—Pediatrics, Executive session—
a] Reading of the minutes; b] Election
of Section Officers and member of Advisory Committee—For Chairman: Edith
M. Lincoln, For Secretary: John D.
Lyttle, For Member of Advisory Committee: Charles Hendee Smith, Pres-

entation of single case reports-a] St. Luke's Hospital—Congenital multiple atresias of the intestine, Peter Duncan (by invitation); b] Mt. Sinai Hospital -A case of hypoglobulinemia, Jerome Greenbaum (by invitation). Discussion opened by Bela Schick; c] Beth Israel Hospital-Prolonged tetany of the newborn, Jacques M. Lewis; d] Willard Parker Hospital-Heart block in diphtheria with recovery, William Kershaw (by invitation). Discussion opened by Cary Eggleston, Edward A. Burkhardt (by invitation); el New York Hospital -A diagnostic problem in a premature infant, Thomas F. Henley (by invitation); f] Babies Hospital-Fever of unknown origin; an unusual solution, Rustin McIntosh; g] New York Post-Graduate Hospital-A case of non-suppurative paniculitis, Vincent DeP. Larkin (by invitation).

May 17-Ophthalmology, Instruction hour 7:00 to 7:45 o'clock-Technique of the preparation of eye specimens from enucleation to microscope, E. B. Burchell (by invitation). I Papers of the evening, 8:00 o'clock-a) A case of spasm of the retinal arteries, C. Ray Franklin (by invitation); b) Recurrence of tobacco-alcohol amblyopia, Frank D. Carroll. ¶ Executive session, 8:30 o'clocka] Reading of the minutes; b] Election of Section Officers and one member of Advisory Committee-For Chairman: Frank C. Keil, For Secretary-Willis S. Knighton; For Member of Advisory Committee: Daniel B. Kirby, ¶ Papers of the evening (continued)-c] The prophylactic use of sulfadiazine in cataract extraction, Jack Guyton (by invitation); d] A case of hemangioma of the choroid, Ralph I. Lloyd; e] A case of seminoma metastatic, Fritz Bloch (by invitation); f] Embryology of the eye-a new method of demonstration, George H. Paff (by invitation); g] Congenital cyst of the optic nerve. Sigmund A. Agatston; h] An original limbal suture for corneal transplants, Vito LaRocca (by invitation).

May 18-Medicine. [Executive session-a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee-For Chairman: Horace Baldwin, For Secretary: William S. Tillett; For Member of Advisory Committee: G. Jarvis Loffin. ¶ Papers of the evening-a] Congenital phlebectasia of lower extremity, M. Kert (by invitation), The Mount Sinai Hospital. Discussion by A. Grishman (by invitation); b] Factors influencing the citric acid metabolism in man, Thomas P. Almy (by invitation), Department of Medicine, New York Hospital. Discussion by Ephriam Shorr (by invitation); cl Chylothorax and chylous ascites, James McCormack (by invitation), Bellevue Hospital. Discussion by William S. Tillett.

May 19-Genito-Urinary Surgery, ¶ Reading of the minutes. I Papers of the evening-al The use of radium in chronic anterior urethral strictures, H. Haig Kasabach (by invitation), b] Laminography as an aid in the visualization of the suprarenal gland, Seymour F. Wilhelm; c] Interesting urologic conditions encountered in the Military Service, Major Thomas P. Sheerer (by invitation). ¶ General discussion. ¶ Executive session-Election of officers; Report of Nominating Committee-For Chairman: John H. Rathbone, For Secretary: E. King Morgan, For Member of Advisory Committee: Major Frank Hamm.

MAY 19—Otolaryngology. ¶Reading of the minutes. ¶Papers of the evening—a] Radiation therapy in otolaryngology (Case presentations: lantern slides), Ira I. Kaplan; b] Variations in the anatomy of the temporal bone (specimens: lantern slide demonstrations), E. B. Burchell (by invitation). ¶General discussion. ¶Executive session—Election of Section Officers and member of Advisory Committee—For Chairman: Victor C. McCuaig, For Secretary: Jackson A. Seward, For Member of Advisory Committee: John Winston Fowlkes.

May 21-Orthopedic Surgery. TExecutive Session-a] Reading of the minutes; b] Election of Section Officers and member of Advisory Committee-For Chairman: Halford Hallock, For Secretary: John R. Cobb, For Member of Advisory Committee-John C. McCauley, Jr. ¶ Presentation of case reports-a] Resection of the elbow for complete ankylosis, Samuel W. Boorstein; b] A case of generalized carcinomatosis in a child, Henry Briggin; c) Translocation of the fibula with its attached structures for pseudoarthrosis of the tibia; fracture of the transplant followed by healing, Joseph Buchman; d] Improvement of carcinomatous metastasis following orchidectomy, John A. Taylor; e] Complications following removal of ruptured nuclei pulposus, Leon Lantzounis; f] Adult club foot, operative correction, Edward M. Winant (by invitation); gl Paget's disease with sarcomatous degeneration, John M. Pendy (by invitation). ¶ General discussion.

MAY 25-Obstetrics and Gynecology, TExecutive session-al Reading of the minutes; b) Election of Section Officers and member of Advisory Committee-For Chairman: Robert J. Lowrie, For Secretary: James P. Marr, For Member of Advisory Committee: William T. Kennedy. [Case reports-a] Antepartum diagnosis of defective cesarean scar, confirmed by operation: a report of two cases, A. J. Rongy; b] Two cases illustrating the effect of the pressure of uterine fibroids on the ureter, S. Wimpfheimer. TPaper of the evening-a] Study of human uterine contractions with the aid of a photoelectric water manometer, I. C. Rubin, S. Feitelberg (by invitation), A. M. Davis (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

APRIL 19—New York Roentgen Society in affiliation with The New York Academy of Medicine. ¶ Papers of the evening—

a] Fibrous dysplasia affecting one, sev-

eral or many bones, Louis Lichtenstein (by invitation); b] Giant cell tumor of bone; its differentiation from lesions confused with it, Henry L. Jaffe (by invitation); c] Radiographic aids in orthopedic surgery, Samuel Jahss (by invitation); d] Posttraumatic osteoporosis (osteochondritis), Joseph Buchman (by invitation). ¶General discussion.

April 22-New York Pathological Society in affiliation with The New York Academy of Medicine. ¶ Papers of the evening-a] Observations on the pathology of osteopetrosis (marble bone disease), Bernard Pines (by invitation); b] The determining influence of the dietary ratio of calcium and phosphorus upon the size of the parathyroid, Herbert C. Stoerk (by invitation), William H. Carnes (by invitation); c] Postmortem findings after dicoumarin therapy, Max Lederer, Edmund Shlevin (by invitation); d] Anti-Rh sera and other aspects of iso-immunization by pregnancy, Philip Levine (by invitation). ¶ Executive session.

May 17—New York Roentgen Society in affiliation with The New York Academy of Medicine. Papers of the evening—a] A simplified method of calculating radium dosage, Bernard Wolff (by invitation); b] Depth-dose measurements in roentgen therapy of 100 to 135 K. V., Carl Braestrup; c] Roentgen therapy in cases of osteomyelitis of the pubis, J. R. Freid; d] Roentgen therapy in cases of pelvic tuberculosis, Harriet C. McIntosh; e] Roentgen therapy in cases of Marie Strumpell spondylitis, Haig H. Kasabach. General discussion. Executive session.

MAY 27—New York Pathological Society in affiliation with The New York Academy of Medicine. TCase presentations—a] Fatal myocarditis in a case of trichinosis, Donald Parker (by invitation), b] Case of telangiostenosis manifesting the clinical picture of periarteritis nodosa, John B. Miale (by invitation),

Jacob Furth. Papers of the evening—a] Pathologic effects of certain common war gases, Capt. Arthur M. Ginzler, M. C.; b] Bronchial adenoma: Distinctive features of its pathology, clinical manifestations, and therapy, Coleman B. Rabin, Harold Neuhof (by invitation). Executive session.

CLINICAL RESEARCH MEETING

May 27-Arranged by the Committee on Medical Education-Medical Division, (Room 20), B. S. Oppenheimer, Presiding Officer-1. The production of a sulfonamide antagonist and a sulfonamide potentiator by the tubercle bacillus, Walsh McDermott, Alice Tracy; 2. Further studies on penicillin as chemotherapeutic agent, Martin Dawson, G. L. Hobby, K. Meyer, E. Chaffee; 3. Certain new considerations in local sulfonamide therapy, Charles L. Fox, Jr.; 4. Studies on the etiology of the renal shutdown following crush injuries, R. J. Bing; 5. The complementfixation test for lymphogranuloma venereum: Results obtained with its use, Arthur W. Grace; 6. Acute infectious lymphocytosis, Carl H. Smith; 7. Probable mechanism by which somatic changes in certain emotional states are mediated, A. T. Milhorat, S. M. Small, E. J. Doty, W. E. Bartels; 8. Physiopathological aspect of muscles in infantile paralysis, J. Moldaver; 9. Neurohormonal regulation of water balance: Studies in patients with diabetes insipidus, Thomas Hodge McGavack; 10. Titration and neutralization of the Western strain of equine encephalomyelitis virus in tissue culture, C. H. Huang; 11. Nitrogen retention, creatinuria, and other effects of the treatment of Simmonds disease, with methyl testosterone, Sidney C. Werner, Randolph West; 12. The relationship between blood concentration and blood volume in cardiac decompensation, Joseph DiPalma, Philip E. Kendall. Surgical Division, Raymond P. Sullivan, Presiding Officer-1. Study of the circulation in clinical shock, A. Cournand, R. L. Riley, E. S. Breed, D. W. Richards, Jr.; 2. Traumatic shock, Magnus I. Gregersen; 3. Renal circulation in shock, Henry Lauson (Bellevue group); 4. The effect of sodium thiosulphate on the blood, Linn J. Boyd, Louis Greenwald, Joseph Litwins; 5. Modification in surgical treatment of herniated nucleus pulposus, Leo M. Davidoff; 6. Plasma-clot suture of peripheral nerves, I. M. Tarlov; 7. A new practical method for the subcutaneous administration of heparin, Leo Loewe, Philip Rosenblatt; 8. The role of the lymphatics in ascending urinary infections, John L. Alley; 9. Test of viability of the gut in local obstructions. John Herrlin, Jr., Thomas Glasser.

Obstetrics and Gynecology, Albert H. Aldridge, Presiding Officer-1. A rapid

pregnancy test (two to six hours), U. J. Salmon, S. H. Geist, C. S. Poole, A. A. Salmon, B.S.; 2. Nutritional deficiency in the etiology of menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension: Treatment with vitamin B complex, Morton S. Biskind, Gerson R. Biskind, Leonard H. Biskind; 3. The concentration of vitamin A in the blood plasma during pregnancy, J. M. Lewis, O. Bodansky, M. C. Lilienfeld; 4. Measurement and recording of intrauterine pressure, Sergei Feitelberg, I. C. Rubin; 5. Vitamin D in human milk, Louis J. Polskin, Benjamin Kramer, Albert E. Sobel; 6. A new experimental laboratory animal, the South African clawed frog (Xenopus laevis): Its use in pregnancy diagnosis, hormone assays and endocrine evaluations, Abner I. Weisman, Christopher W. Coates.

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